



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 139526

TO: Shaojia A Jiang
Location: REM 4B18 4cD4
Art Unit: 1617
December 3, 2004

Case Serial Number: 09/977059

From: P. Sheppard
Location: Remsen Building
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Search Notes

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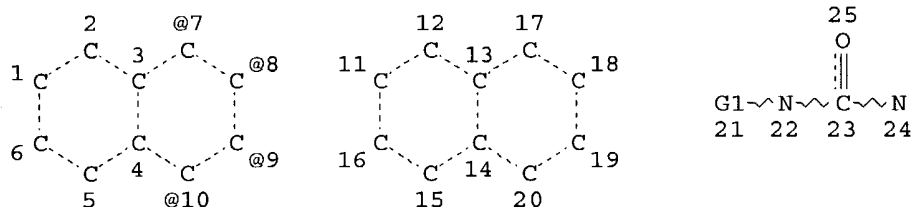
FILE COVERS 1907 - 3 Dec 2004 VOL 141 ISS 23
FILE LAST UPDATED: 1 Dec 2004 (20041201/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L1 STR



VAR G1=7/8/9/10

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DEFAULT ECLEVEL IS LIMITED

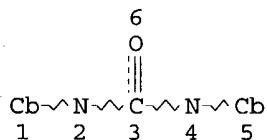
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RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L3 STR



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GGCAT IS PCY AT 5

DEFAULT ECLEVEL IS LIMITED

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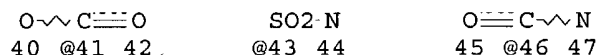
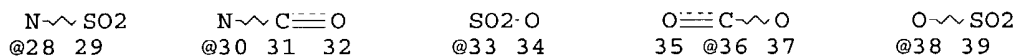
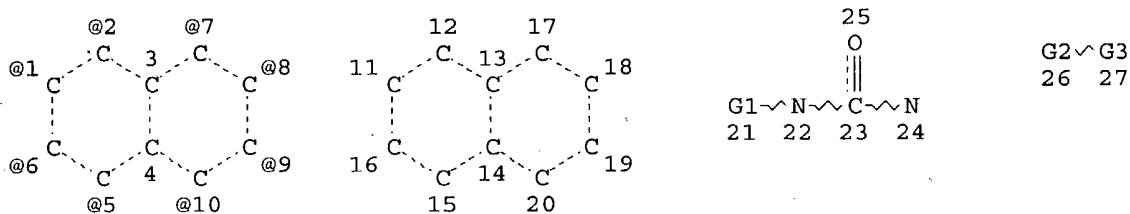
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NUMBER OF NODES IS 6

STEREO ATTRIBUTES: NONE

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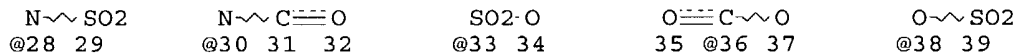
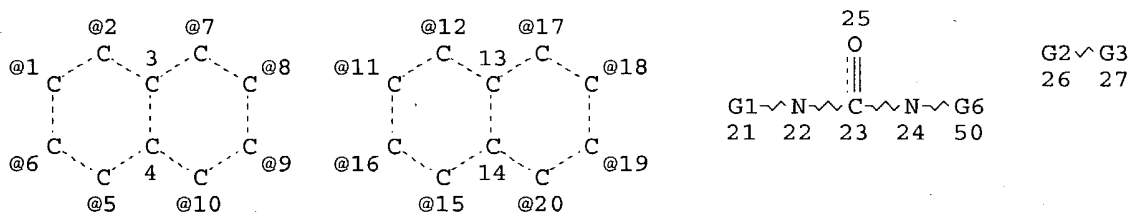
L9 STR



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VAR G3=28/30/33/36/38/41/43/46
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE
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L12 STR



VAR G1=7/8/9/10
VAR G2=1/2/5/6
VAR G3=28/30/33/36/38/41/43/46
VAR G4=17/18/19/20
VAR G5=28/30/33/36/38/41/43/46
VAR G6=11/12/15/16
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 50

STEREO ATTRIBUTES: NONE

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OR ?DRUG? OR ?PHARMA?)
L18 62 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 NOT L17
L20 STR

N=N
1 2

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 2

STEREO ATTRIBUTES: NONE

L22 277 SEA FILE=REGISTRY SUB=L8 SSS FUL L1 NOT L20
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OR ?DRUG? OR ?PHARMA?)
L27 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L26 NOT (L17 OR L18)

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=> d ibib abs hitstr l27 1-15

L27 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:740458 HCAPLUS

DOCUMENT NUMBER: 141:254541

TITLE: Small-molecule inhibitors of angiogenin and RNases and
in vivo and in vitro methods of using same

INVENTOR(S): Shapiro, Robert; Jenkins, Jeremy L.; Kao, Richard Y.
T.; Latham, Gary J.

PATENT ASSIGNEE(S): Ambion, Inc., USA

SOURCE: PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004076640	A2	20040910	WO 2004-US5663	20040225
W:	AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,			

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 MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
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PRIORITY APPLN. INFO.:

US 2003-449912P

P 20030225

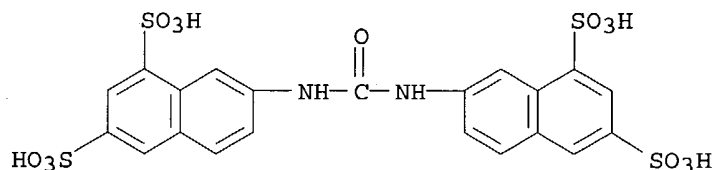
AB Lead compds. were obtained in a high throughput screen (HTS) of angiogenin (ANG; a potent inducer of angiogenesis) enzyme activity, an RNase. One lead was shown to delay appearance of tumors in an animal tumor system, and to reduce the number of animals having tumors. Several lead compound analogs were even more potent inhibitors of ANG activity compared to the original leads, and two were also found to have greater affinity for ANG than for pancreatic RNase. Other embodiments disclose a method comprising obtaining a RNase inhibitor and a composition; and admixing the RNase inhibitor and the composition to form an admixt., wherein a RNase that may be present in the admixt. is inhibited.

IT 157872-23-6, NCI 12857

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (antitumor inhibitors of angiogenin and RNases)

RN 157872-23-6 HCAPLUS

CN 1,3-Naphthalenedisulfonic acid, 7,7'-(carbonyldiimino)bis- (9CI) (CA
 INDEX NAME)



L27 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:654173 HCAPLUS

DOCUMENT NUMBER: 141:342930

TITLE: In vitro and in vivo prevention of HIV protease inhibitor-induced insulin resistance by a novel small molecule insulin receptor activator

AUTHOR(S): Cheng, Mingshan; Chen, Seiyu; Schow, Steven R.; Mancham, Vara Prasad; Spevak, Wayne R.; Cristobal, Cristina P.; Shi, Songyuan; Macsata, Robert W.; Lum, Robert T.; Goldfine, Ira D.; Keck, James G.

CORPORATE SOURCE: → Telik, Inc., Palo Alto, CA, 94304, USA

SOURCE: Journal of Cellular Biochemistry (2004), 92(6), 1234-1245

CODEN: JCEBD5; ISSN: 0730-2312

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Protease inhibitor (PI) therapy for the treatment of patients infected with human immunodeficiency virus is frequently associated with insulin resistance and diabetic complications. These adverse effects of PI treatment result to a large extent from their inhibition of insulin-stimulated glucose transport. Insulin receptor (IR) activators that enhance the insulin signaling pathway could be effective in treating this resistance. However, there are no agents reported that reverse inhibition of insulin action by PIs. Herein, we describe the effects of TLK19781. This compound is a non-peptide, small mol., activator of the IR. We now report in cultured cells, made insulin resistant HIV by PI

same as invention here

treatment, that TLK19781 both increased the content of insulin-stimulated GLUT4 at the plasma membrane, and enhanced insulin-stimulated glucose transport. In addition, oral administration of TLK19781 with the PI, indinavir improved glucose tolerance in rats made insulin resistant. These results suggest, therefore, that IR activators such as TLK19781 may be useful in treating the insulin resistance associated with PIs.

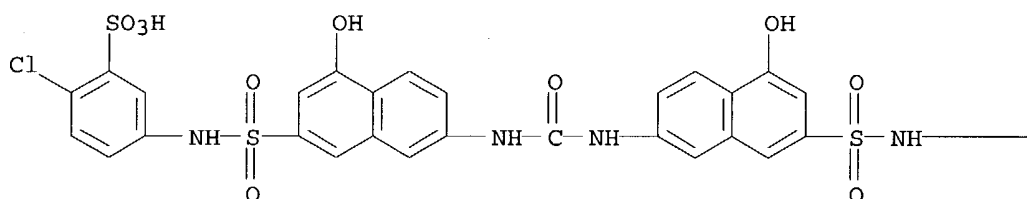
IT 309932-60-3

RL: PAC (Pharmacological activity); BIOL (Biological study)
(prevention of HIV protease inhibitor-induced insulin resistance by a novel small mol. insulin receptor activator)

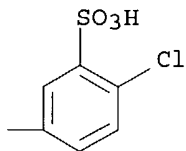
RN 309932-60-3 HCAPLUS

CN Benzenesulfonic acid, 3,3'-[carbonylbis[imino(4-hydroxy-7,2-naphthalenediyl)sulfonylimino]]bis[6-chloro- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:924974 HCAPLUS

DOCUMENT NUMBER: 140:138734

TITLE: Suramin and Suramin Analogues Inhibit Merozoite Surface Protein-1 Secondary Processing and Erythrocyte Invasion by the Malaria Parasite Plasmodium falciparum
AUTHOR(S): Fleck, Suzanne L.; Birdsall, Berry; Babon, Jeffrey; Dluzewski, Anton R.; Martin, Stephen R.; Morgan, William D.; Angov, Evelina; Kettleborough, Catherine A.; Feeney, James; Blackman, Michael J.; Holder, Anthony A.

CORPORATE SOURCE: Medical Research Council Technology, London, NW7 1AD, UK

SOURCE: Journal of Biological Chemistry (2003), 278(48), 47670-47677

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Malarial merozoites invade erythrocytes; and as an essential step in this invasion process, the 42-kDa fragment of Plasmodium falciparum merozoite surface protein-1 (MSP142) is further cleaved to a 33-kDa N-terminal

polypeptide (MSP133) and an 19-kDa C-terminal fragment (MSP119) in a secondary processing step. Suramin was shown to inhibit both merozoite invasion and MSP142 proteolytic cleavage. This polysulfonated naphthylurea bound directly to recombinant *P. falciparum* MSP142 ($K_d = 0.2 \mu\text{M}$) and to *Plasmodium vivax* MSP142 ($K_d = 0.3 \mu\text{M}$) as measured by fluorescence enhancement in the presence of the protein and by isothermal titration calorimetry. Suramin bound only slightly less tightly to the *P. vivax* MSP133 ($K_d = 1.5 \mu\text{M}$) secondary processing product (fluorescence measurements), but very weakly to MSP119 (K_d .apprx. 15 mM) (NMR measurements). Several residues in MSP119 were implicated in the interaction with suramin using NMR measurements. A series of sym. suramin analogs that differ in the number of aromatic rings and substitution patterns of the terminal naphthylamine groups was examined in invasion and processing assays. Two classes of analog with either two or four bridging rings were found to be active in both assays, whereas two other classes without bridging rings were inactive. We propose that suramin and related compds. inhibit erythrocyte invasion by binding to MSP1 and by preventing its cleavage by the secondary processing protease. The results indicate that enzymic events during invasion are suitable targets for **drug** development and validate the novel concept of an inhibitor binding to a macromol. substrate to prevent its proteolysis by a protease.

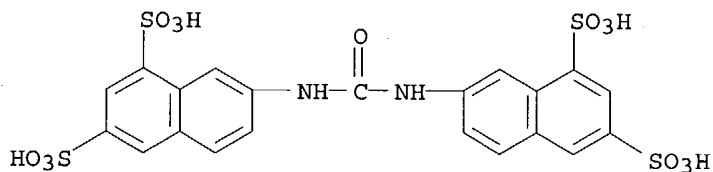
IT 157872-23-6, CPD 1

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(CPD 1; suramin and suramin analogs inhibit merozoite surface protein-1 secondary processing and erythrocyte invasion by the malaria parasite *Plasmodium falciparum*)

RN 157872-23-6 HCAPLUS

CN 1,3-Naphthalenedisulfonic acid, 7,7'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



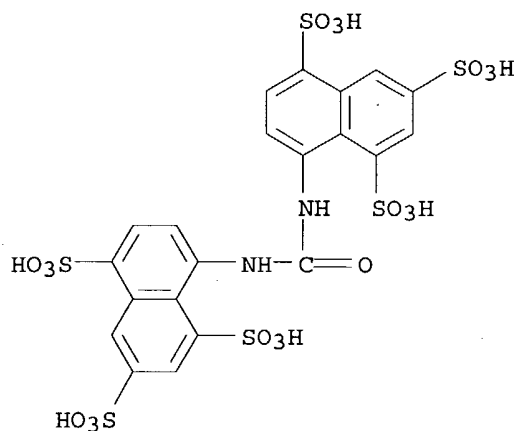
IT 104954-44-1, CPD 2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(CPD 2; suramin and suramin analogs inhibit merozoite surface protein-1 secondary processing and erythrocyte invasion by the malaria parasite *Plasmodium falciparum*)

RN 104954-44-1 HCAPLUS

CN 1,3,5-Naphthalenetrisulfonic acid, 8,8'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



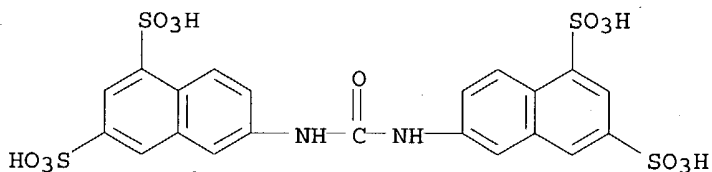
IT 104954-42-9, CPD 4

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(CPD 4; suramin and suramin analogs inhibit merozoite surface protein-1
secondary processing and erythrocyte invasion by the malaria parasite
Plasmodium falciparum)

RN 104954-42-9 HCAPLUS

CN 1,3-Naphthalenedisulfonic acid, 6,6'-(carbonyldiimino)bis- (9CI) (CA
INDEX NAME)



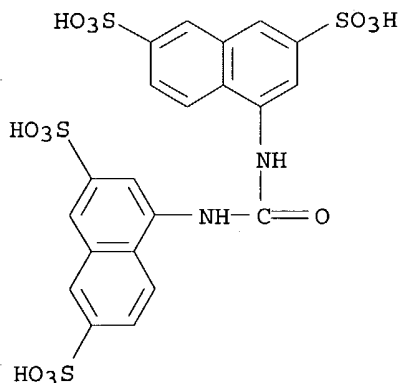
IT 104954-43-0, CPD 6

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(CPD 6; suramin and suramin analogs inhibit merozoite surface protein-1
secondary processing and erythrocyte invasion by the malaria parasite
Plasmodium falciparum)

RN 104954-43-0 HCAPLUS

CN 2,7-Naphthalenedisulfonic acid, 4,4'-(carbonyldiimino)bis- (9CI) (CA
INDEX NAME)



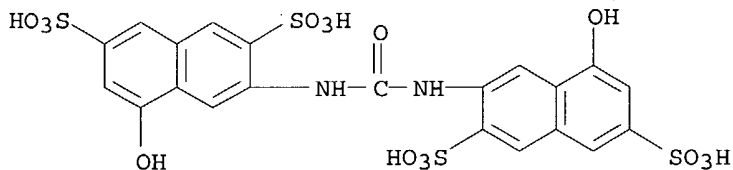
IT 104954-45-2, CPD 7

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(CPD 7; suramin and suramin analogs inhibit merozoite surface protein-1 secondary processing and erythrocyte invasion by the malaria parasite *Plasmodium falciparum*)

RN 104954-45-2 HCAPLUS

CN 2,7-Naphthalenedisulfonic acid, 3,3'-(carbonyldiimino)bis[5-hydroxy- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:656575 HCAPLUS

DOCUMENT NUMBER: 139:197476

TITLE: Preparation of aryl heterocyclyl ureas with raf kinase and angiogenesis inhibiting activity

INVENTOR(S): Dumas, Jacques; Scott, William J.; Elting, James; Hatoum-Makdad, Holia

PATENT ASSIGNEE(S): Bayer Corporation, USA

SOURCE: PCT Int. Appl., 142 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

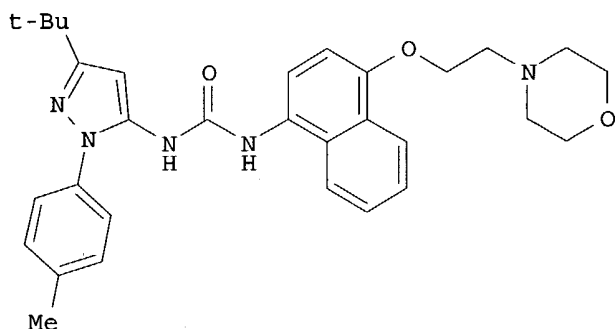
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WO 2003068223	A1	20030821	WO 2003-US4102	20030211
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UG, US, UZ, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2004023961 A1 20040205 US 2003-361844 20030211

PRIORITY APPLN. INFO.: US 2002-354948P P 20020211

GI



AB 283 Of the title ureas useful for treating diseases mediated by raf kinase and diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes, were claimed. Synthesis of 6 ureas such as I was described. Thus, reacting 3-(tert-butyl)-1-(4-methylphenyl)pyrazole-5-ylamine with 4-(2-morpholin-4-ylethoxy)naphthylamine (prepns. given) and CDI in CH₂Cl₂ afforded 80% I which showed IC₅₀ of < 1 μM in in vitro raf kinase and in in vitro Flk-1 ELISA assay.

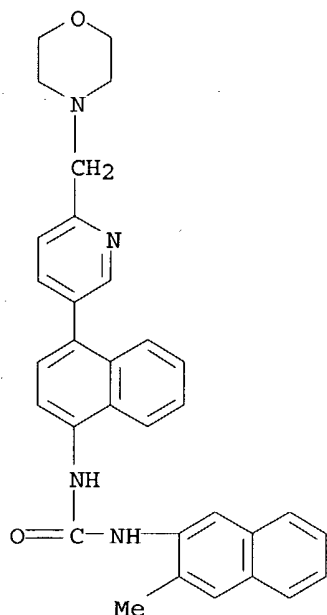
IT 294850-06-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of aryl heterocyclyl ureas with raf kinase and angiogenesis inhibiting activity)

RN 294850-06-9 HCAPLUS

CN Urea, N-(3-methyl-2-naphthalenyl)-N'-[4-[6-(4-morpholinylmethyl)-3-pyridinyl]-1-naphthalenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:221509 HCAPLUS

DOCUMENT NUMBER: 138:231790

TITLE: Methods using aromatic heterocyclcyl compounds for treating cytokine-mediated diseases

INVENTOR(S): Moss, Neil; Regan, John R.

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 175 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022273	A1	20030320	WO 2002-US28615	20020909
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003060455	A1	20030327	US 2002-237306	20020909
EP 1427412	A1	20040616	EP 2002-797884	20020909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
PRIORITY APPLN. INFO.:			US 2001-318958P	P 20010913
			WO 2002-US28615	W 20020909

OTHER SOURCE(S): MARPAT 138:231790

AB Methods are disclosed for treating acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, sepsis, chronic obstructive pulmonary disease, traumatic arthritis, congestive heart failure and restenosis percutaneous transluminal coronary angioplasty, known to be cytokine mediated, using aromatic heterocyclic compds. described in WO 00/55139.

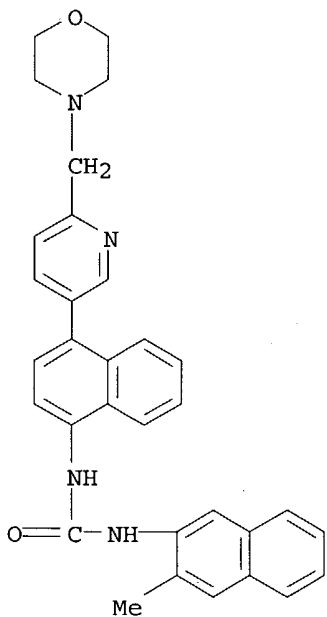
IT 294850-06-9 294850-06-9D, derivs. 501365-36-2
501365-36-2D, derivs. 501365-41-9 501365-41-9D
, derivs. 501365-54-4 501365-54-4D, derivs.

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(aromatic heterocyclyl compds. for treating cytokine-mediated diseases)

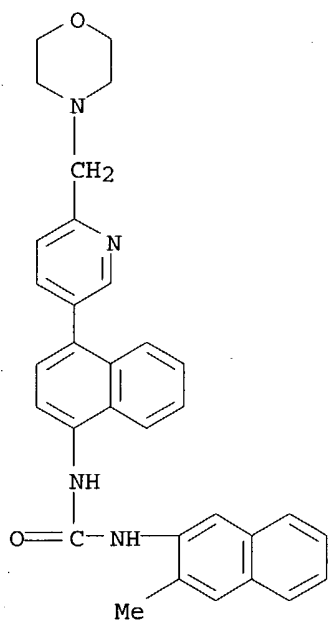
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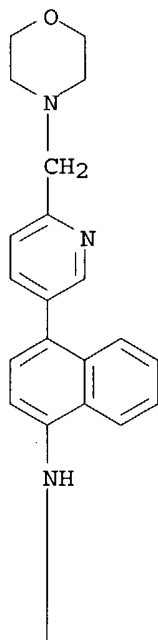
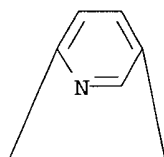
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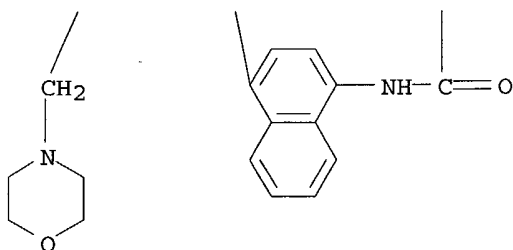


RN 501365-36-2 HCAPLUS
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PAGE 1-A

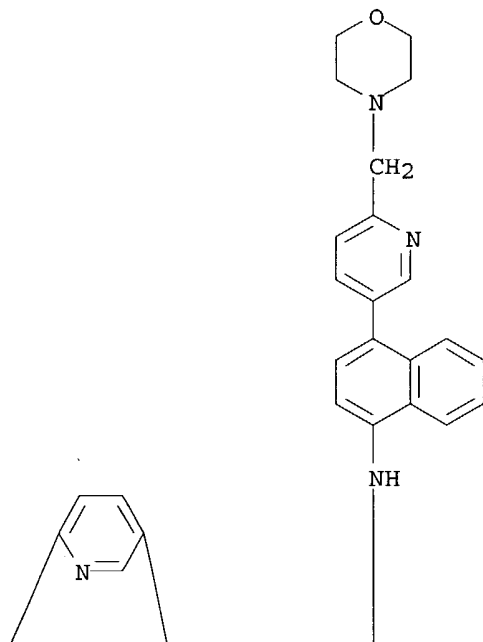


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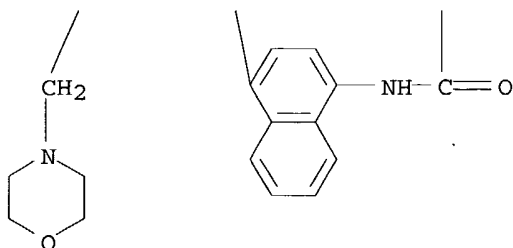


RN 501365-36-2 HCAPLUS
 CN Urea, N,N'-bis[4-[6-(4-morpholinylmethyl)-3-pyridinyl]-1-naphthalenyl]-(9CI) (CA INDEX NAME)

PAGE 1-A



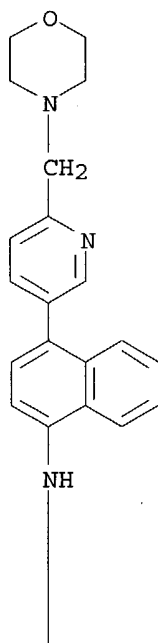
PAGE 2-A



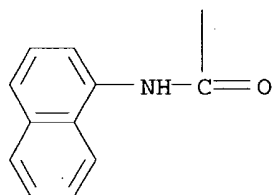
RN 501365-41-9 HCAPLUS
 CN Urea, N-[4-[6-(4-morpholinylmethyl)-3-pyridinyl]-1-naphthalenyl]-N'-1-

naphthalenyl- (9CI) (CA INDEX NAME)

PAGE 1-A

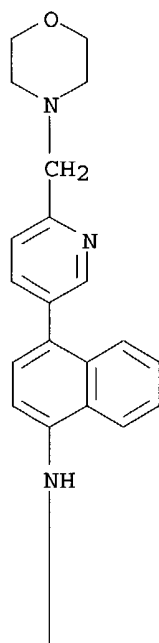


PAGE 2-A

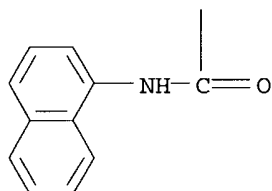


RN 501365-41-9 HCAPLUS
 CN Urea, N-[4-[6-(4-morpholinylmethyl)-3-pyridinyl]-1-naphthalenyl]-N'-1-naphthalenyl- (9CI) (CA INDEX NAME)

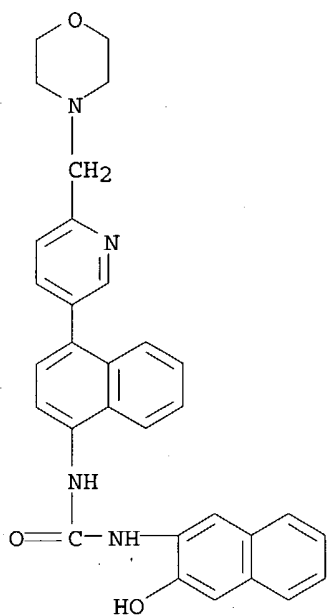
PAGE 1-A



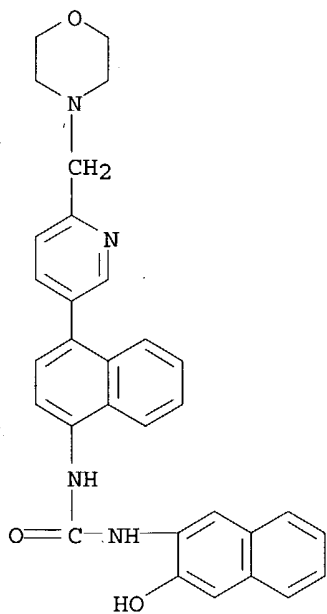
PAGE 2-A



RN 501365-54-4 HCAPLUS
 CN Urea, N-(3-hydroxy-2-naphthalenyl)-N'-[4-[6-(4-morpholinylmethyl)-3-pyridinyl]-1-naphthalenyl]- (9CI) (CA INDEX NAME)



RN 501365-54-4 HCAPLUS
 CN Urea, N-(3-hydroxy-2-naphthalenyl)-N'-[4-[6-(4-morpholinylmethyl)-3-pyridinyl]-1-naphthalenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:212343 HCAPLUS

DOCUMENT NUMBER: 139:129772

TITLE: A novel mechanism for inhibition of HIV-1 reverse transcriptase

AUTHOR(S): Skillman, A. Geoffrey; Maurer, Karl W.; Roe, Diana C.; Stauber, Margaret J.; Eargle, Dolan; Ewing, Todd J. A.; Muscate, Angelika; Davioud-Charvet, Elisabeth; Medaglia, Maxine V.; Fisher, Robert J.; Arnold, Edward; Gao, Hong-Qiang; Buckheit, Robert; Boyer, Paul L.; Hughes, Stephen H.; Kuntz, Irwin D.; Kenyon, George L.

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, CA, 94143-0446, USA

SOURCE: Bioorganic Chemistry (2002), 30(6), 443-458
CODEN: BOCMBM; ISSN: 0045-2068

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

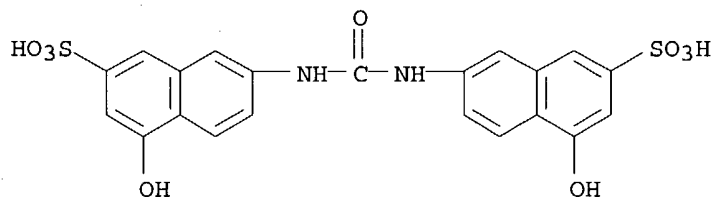
OTHER SOURCE(S): CASREACT 139:129772

AB The human immunodeficiency virus (HIV) epidemic is an important **medical** problem. Although combination **drug** regimens have produced dramatic decreases in viral load, current **therapies** do not provide a cure for HIV infection. We have used structure-based design and combinatorial **medicinal** chemical to identify potent and selective HIV-1 reverse transcriptase (RT) inhibitors that may work by a mechanism distinct from that of current HIV **drugs**. The most potent of these compds. (compound 4, 2-naphthalenesulfonic acid, 4-hydroxy-7-[[[5-hydroxy-6-[(4-cinnamylphenyl)azo]-7-sulfo-2-naphthalenyl]amino]carbonyl]amino]-3-[(4-cinnamylphenyl)azo], disodium salt) has an IC50 of 90 nM for inhibition of polymerase chain extension, a Kd of 40 nM for inhibition of DNA-RT binding, and an IC50 of 25-100 nM for inhibition of RNaseH cleavage. The parent compound (1) was as effective against 10 nucleoside and non-nucleoside resistant HIV-1 RT mutants as it was against the wild-type enzyme. Compound 4 inhibited HIV-1 RT and murine leukemia virus (MLV) RT, but it did not inhibit T4 DNA polymerase, T7 DNA polymerase, or the Klenow fragment at concns. up to 200 nM. Finally, compound 4 protected cells from HIV-1 infection at a concentration more than 40 times lower than the concentration at which it caused cellular toxicity.

IT 134-47-4, Carbonyl j
RL: RCT (Reactant); RACT (Reactant or reagent)
(novel mechanism for inhibition of HIV-1 reverse transcriptase and murine leukemia virus reverse transcriptase)

RN 134-47-4 HCAPLUS

CN 2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis[4-hydroxy- (9CI)
(CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:293499 HCAPLUS

DOCUMENT NUMBER: 136:304094

TITLE: Insulin receptor activators for the treatment of metabolic disorders in humans resulting from treatment of HIV infection with HIV protease inhibitors

INVENTOR(S): Manchem, Prasad V. V. S. V.; Lum, Robert T.; Schow, Steven R.
 PATENT ASSIGNEE(S): Telik, Inc., USA
 SOURCE: PCT Int. Appl., 48 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

same invention info

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030514	A2	20020418	WO 2001-US42733	20011010
WO 2002030514	A3	20030731		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
FR 2814953	A1	20020412	FR 2001-13040	20011010
CA 2421622	AA	20020415	CA 2001-2421622	20011010
AU 2002011922	A5	20020422	AU 2002-11922	20011010
EP 1355698	A2	20031029	EP 2001-980019	20011010
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004510831	T2	20040408	JP 2002-533952	20011010
PRIORITY APPLN. INFO.:			US 2000-239636P	P 20001011
			WO 2001-US42733	W 20011010

OTHER SOURCE(S): MARPAT 136:304094

AB The invention comprises the use of insulin receptor activating compds., optionally in conjunction with insulin, for the treatment of HIV protease inhibitor-induced metabolic disorders. Any insulin receptor activating compds. suitable for the practice of the invention and other addnl. dinaphthalene urea derivs. are disclosed. Methods of treating a person suffering from HIV protease inhibitor-induced metabolic disorders such as lipodystrophy, hypertriglyceridemia, insulin resistance, hyperglycemia, diabetes and ketoacidosis are also provided.

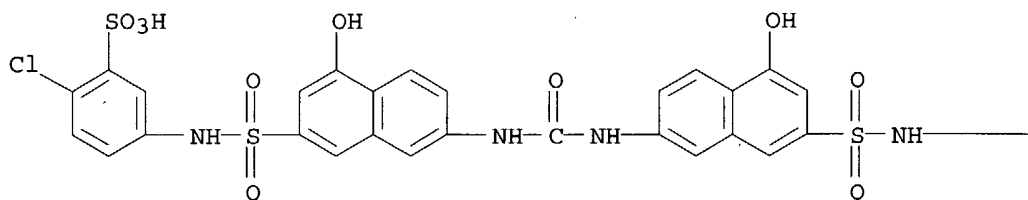
IT 309932-60-3P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (insulin receptor activators for treatment of metabolic disorders in humans resulting from treatment of HIV infection with HIV protease inhibitors)

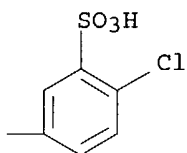
RN 309932-60-3 HCAPLUS

CN Benzenesulfonic acid, 3,3'-[carbonylbis(imino(4-hydroxy-7,2-naphthalenediyl)sulfonylimino)]bis[6-chloro- (9CI) (CA INDEX NAME)

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IT 309932-18-1P

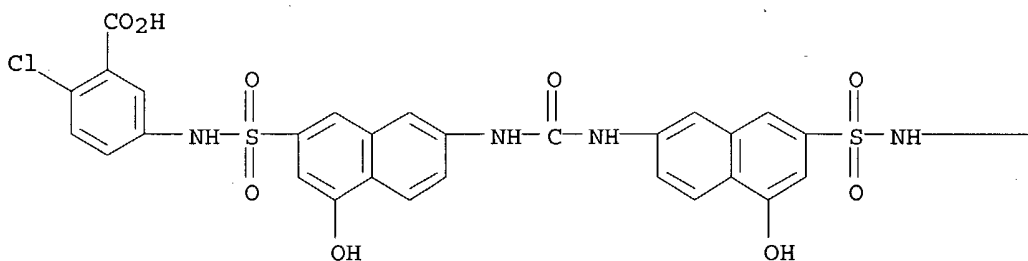
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(insulin receptor activators for treatment of metabolic disorders in humans resulting from treatment of HIV infection with HIV protease inhibitors)

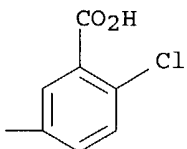
RN 309932-18-1 HCAPLUS

CN Benzoic acid, 3,3'-[carbonylbis[imino(4-hydroxy-7,2-naphthalenediyl)sulfonylimino]]bis[6-chloro- (9CI) (CA INDEX NAME)

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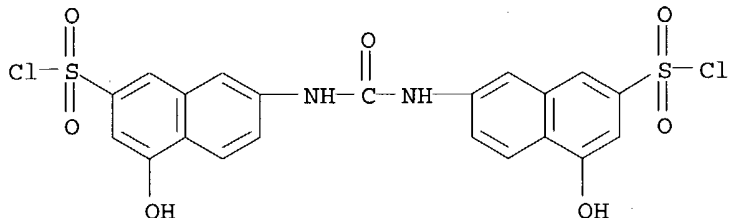
IT 309933-11-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(insulin receptor activators for treatment of metabolic disorders in humans resulting from treatment of HIV infection with HIV protease inhibitors)

inhibitors)

RN 309933-11-7 HCAPLUS

CN 2-Naphthalenesulfonyl chloride, 7,7'-(carbonyldiimino)bis[4-hydroxy- (9CI)
(CA INDEX NAME)

L27 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:513460 HCAPLUS

DOCUMENT NUMBER: 133:317215

TITLE: Carbonyl J Derivatives: A New Class of HIV-1 Integrase Inhibitors

AUTHOR(S): Maurer, Karl; Tang, Ann H.; Kenyon, George L.;
Leavitt, Andrew D.CORPORATE SOURCE: Department of Laboratory Medicine, University of
California, San Francisco, CA, USASOURCE: Bioorganic Chemistry (2000), 28(3), 140-155
CODEN: BOCMBM; ISSN: 0045-2068

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 133:317215

AB Integration of a DNA copy of the HIV-1 genome is required for viral replication and pathogenicity, and this highly specific mol. process is mediated by the virus-encoded integrase protein. The requirement for integration, combined with the lack of a known analogous process in mammalian cells, makes integrase an attractive target for **therapeutic** inhibitors of HIV-1 replication. While many reports of HIV-1 IN inhibitors exist, no such compds. have yet emerged to treat HIV-1 infection. As such, new classes of integrase inhibitors are needed. We have combined mol. modeling and combinatorial chemical to identify and develop a new class of HIV-1 integrase inhibitors, the Carbonyl J [N,N'-bis-2-(5-hydroxy-7-naphthalenesulfonic acid)urea] derivs. This new class includes a number of compds. with sub-micromolar IC50 values for inhibiting purified HIV-1 integrase in vitro. Herein we describe the chemical characteristics that are important for integrase inhibition and cell toxicity within the Carbonyl J derivs. (c) 2000 Academic Press.

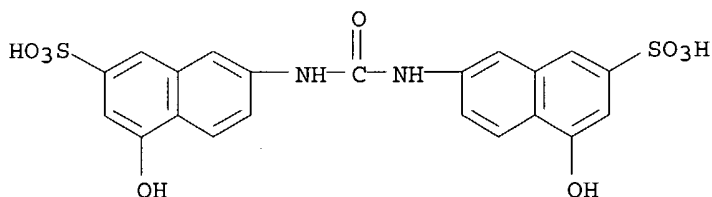
IT 134-47-4P, Carbonyl J

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(Carbonyl J; carbonyl J derivs.: a new class of HIV-1 integrase inhibitors)

RN 134-47-4 HCAPLUS

CN 2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis[4-hydroxy- (9CI)
(CA INDEX NAME)



L27 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:421642 HCAPLUS

DOCUMENT NUMBER: 131:58658

TITLE: Inhibition of raf kinase using symmetrical and unsymmetrical substituted diphenyl ureas

INVENTOR(S): Miller, Scott; Osterhout, Martin; Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Gunn, David; Rodriguez, Mareli; Wang, Ming

PATENT ASSIGNEE(S): Bayer Corporation, USA

SOURCE: PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

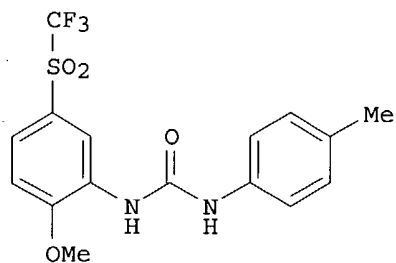
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932436	A1	19990701	WO 1998-US26081	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315646	AA	19990701	CA 1998-2315646	19981222
AU 9919054	A1	19990712	AU 1999-19054	19981222
AU 763024	B2	20030710		
EP 1049664	A1	20001108	EP 1998-963809	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200002616	T2	20001121	TR 2000-200002616	19981222
TR 200100874	T2	20010621	TR 2001-200100874	19981222
JP 2001526258	T2	20011218	JP 2000-525373	19981222
BR 9814375	A	20020521	BR 1998-14375	19981222
NZ 505843	A	20030630	NZ 1998-505843	19981222
EP 1449834	A2	20040825	EP 2003-26051	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NO 2000003230	A	20000821	NO 2000-3230	20000621
BG 104599	A	20010330	BG 2000-104599	20000712
PRIORITY APPLN. INFO.:				
			US 1997-996344	A 19971222
			EP 1998-963809	A3 19981222
			WO 1998-US26081	W 19981222

OTHER SOURCE(S): MARPAT 131:58658

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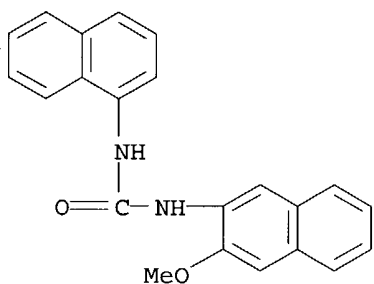
AB The invention relates to the use of a group of aryl ureas ANHCONHB [I; A = certain (un)substituted Ph, pyridinyl, or thien-2-yl groups; B = certain (un)substituted mono- to tricyclic aryl or heteroaryl groups] in treating raf-mediated diseases, and **pharmaceutical** compns. for use in such **therapy**. A subset of I are novel and are claimed per se. Approx. 160 invention compds. and numerous intermediates were prepared For instance, reaction of tolyl isocyanate with 2-methoxy-5-(trifluoromethanesulfonyl)aniline in EtOAc gave title compound II. In an in vitro raf kinase assay, all compds. displayed IC50 values between 1 nM and 10 μ M.

IT 228400-96-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of sym. and unsym. substituted di-Ph ureas with inhibitory effects on tumors mediated by raf kinase)

RN 228400-96-2 HCAPLUS

CN Urea, N-(3-methoxy-2-naphthalenyl)-N'-1-naphthalenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:509345 HCAPLUS

DOCUMENT NUMBER: 129:144864

TITLE: Modulators of insulin receptor activity, screening, and **therapeutic** use

INVENTOR(S): Kauvar, Lawrence M.; Sportsman, Richard; Villar, Hugo O.; Spevak, Wayne R.; Kohanski, Ron A.; Satyam, Apparao; Koehler, Ryan

PATENT ASSIGNEE(S): Terrapin Technologies, Inc., USA

SOURCE: PCT Int. Appl., 77 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9832017	A2	19980723	WO 1998-US801	19980115
WO 9832017	A3	19990225		
W: AU, BA, CA, CU, GH, GM, GW, ID, JP, LC, SL, YU, ZW				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5830918	A	19981103	US 1997-784857	19970115
US 5851988	A	19981222	US 1997-784854	19970115
US 6329431	B1	20011211	US 1997-916088	19970821
CA 2278023	AA	19980723	CA 1998-2278023	19980115
AU 9860266	A1	19980807	AU 1998-60266	19980115
EP 960335	A2	19991201	EP 1998-903515	19980115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002512685	T2	20020423	JP 1998-534532	19980115
US 2002016367	A1	20020207	US 2001-961179	20010921
US 2003078188	A1	20030424	US 2001-999762	20011025

PRIORITY APPLN. INFO.:

US 1997-784854	A	19970115
US 1997-784855	A	19970115
US 1997-784857	A	19970115
US 1997-825269	A	19970327
US 1997-916088	A	19970821
WO 1998-US801	W	19980115
US 1998-88507	B1	19980601

OTHER SOURCE(S): MARPAT 129:144864

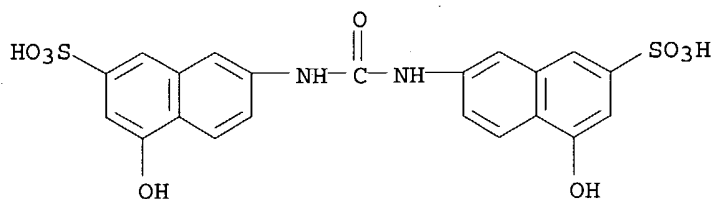
AB Methods to identify compds. which have ≥ 1 characteristic selected from the group consisting of a composition that (a) modulates the kinase activity of insulin receptor; and/or (b) potentiates the insulin activation of insulin receptor; and/or (c) potentiates the stimulation by insulin of cellular glucose uptake; and/or (d) stimulates the uptake of glucose in cells displaying the insulin receptor; and/or (e) lowers blood glucose in diabetic subjects; and/or (f) stimulates IRS-1 phosphorylation; and/or (g) stimulates PI3 kinase activity; and/or (h) stimulates GLUT-4 translocation; are described. Successful substances having such characteristics alter the conformation of the two-lobed cytoplasmic kinase domain or preferentially bind sites which have been identified as modulator binding sites in the insulin receptor β chain. Also, modulation of the activity of the insulin receptor, enhancement of glucose uptake by cells, and other effects significant in the control and management of diabetes are accomplished using [Ari(A)(R)mlinker]nAr(A)(R)m (Ar = aromatic moiety; A = proton-accepting substituent; R = non-interfering substituent; m = 0-2 n = 1-6; linker = CH₂, N=N, CH=CH, NHCO, NHCONH or isostere thereof; when n = 1, ≥ 1 Ar must comprise ≥ 2 fused aromatic rings) (I). I can also be used for structure-activity studies to identify features responsible for the relevant activities.

IT 20324-87-2

RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; modulators of insulin receptor activity, screening, and therapeutic use)

RN 20324-87-2 HCAPLUS

CN 2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis[4-hydroxy-, disodium salt (9CI) (CA INDEX NAME)



●2 Na

L27 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:708311 HCAPLUS

DOCUMENT NUMBER: 121:308311

TITLE: Use of dinaphthalenes compounds as antiproliferative agents

INVENTOR(S): Harris, Adrian Llewelyn; Bicknell, Roy; Herlihy, Walter Curtin, Jr.; Rusche, James Robert; Witt, Daniel Parker

PATENT ASSIGNEE(S): Imperial Cancer Research Technology Ltd., UK

SOURCE: PCT Int. Appl., 128 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

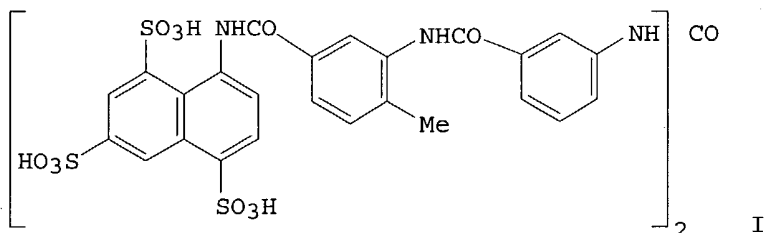
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9413277	A2	19940623	WO 1993-GB2493	19931206
WO 9413277	A3	19940804		
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9456549	A1	19940704	AU 1994-56549	19931206
PRIORITY APPLN. INFO.:			GB 1992-25475	A 19921205
			WO 1993-GB2493	W 19931206

OTHER SOURCE(S): MARPAT 121:308311

GI



AB Comps. such as suramin (I) or its derivs. or a **pharmaceutically** acceptable salt, ester, salt of such ester or amide of such compds., are used in the manufacture of a **medicament** for use in reducing undesired

angiogenesis, treating cancer, treating fibrotic disease, or treating diseases benefiting from antagonism of the action of fibroblast, vascular endothelial and transforming growth factors. An example is given of inhibition of Swiss 3T3 fibroblast and capillary endothelial cell 3H-methylthymidine uptake by I and other compds. **Pharmaceutical** compns. of I and derivs. are given.

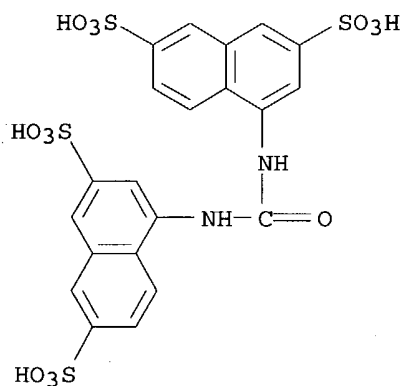
IT 104954-43-0P 157872-23-6P

RL: PREP (Preparation)

(preparation of, as antiproliferative and angiogenesis-decreasing compound)

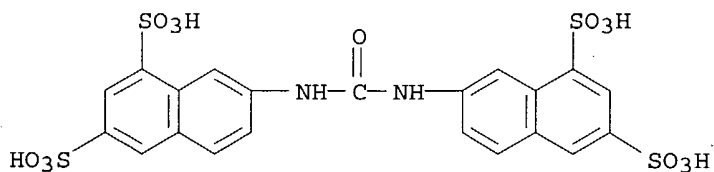
RN 104954-43-0 HCAPLUS

CN 2,7-Naphthalenedisulfonic acid, 4,4'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



RN 157872-23-6 HCAPLUS

CN 1,3-Naphthalenedisulfonic acid, 7,7'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



L27 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:621032 HCAPLUS

DOCUMENT NUMBER: 121:221032

TITLE: A structure-activity analysis of antagonism of the growth factor and angiogenic activity of basic fibroblast growth factor by suramin and related polyanions

AUTHOR(S): Braddock, P. S.; Hu, D. -E.; Fan, T. -P. D.; Stratford, I. J.; Harris, A. L.; Bicknell, R.

CORPORATE SOURCE: John Radcliffe Hosp., Univ. Oxford, Oxford, OX3 9DU, UK

SOURCE: British Journal of Cancer (1994), 69(5), 890-8
CODEN: BJCAAI; ISSN: 0007-0920

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The ability of a series of polysulfonated naphthylureas structurally related to suramin to inhibit basic fibroblast growth factor (bFGF) or serum-stimulated growth of endothelial cells [either large vessel, human

umbilical vein endothelial cells (HUVEC) or microvascular, bovine adrenal capillary endothelial (BACE) cells] and angiogenesis in vivo has been examined. The polyanions encompassed two main structural variations, namely the number of aromatic amide groups intervening between two terminal naphthyl rings and/or variation in the substitution pattern of the naphthyl rings. The polyanions were either inactive (group I) or inhibited (group II) bFGF-stimulated uptake of [3H]methylthymidine by BACE cells. Group I compds. shared a common structural feature in that they were simple binaphthyl-substituted ureas. In contrast, group II compds. all had an extended multiple ring structure with at least two aromatic groups intervening between the two terminal naphthyl rings. Compds. with either two or four intervening groups were equipotent in blocking bFGF in vitro. However, compds. with two bridging aromatic groups were 5- to 10-fold less toxic than suramin in mice, suggesting a potential for an improved **therapeutic** ratio. The ability of the polyanions to block bFGF-driven endothelial cell proliferation in vitro correlated with antiangiogenic activity in vivo as shown by use of the rat sponge angiogenesis model. These observations could substantially widen the anti-tumor **therapeutic** opportunities for this class of compound

IT 104954-42-9 104954-43-0 104954-44-1

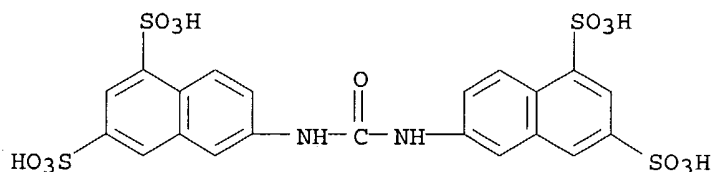
104954-45-2 157872-23-6 158195-72-3

RL: BIOL (Biological study)

(fibroblast growth factor and angiogenesis inhibition by, antitumor activity and structure in relation to)

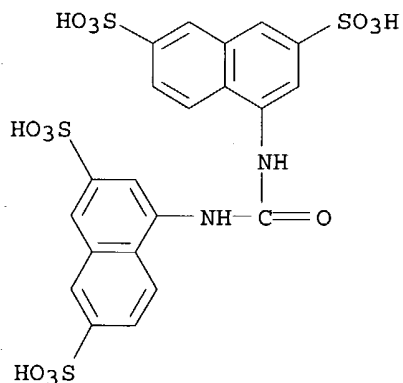
RN 104954-42-9 HCAPLUS

CN 1,3-Naphthalenedisulfonic acid, 6,6'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



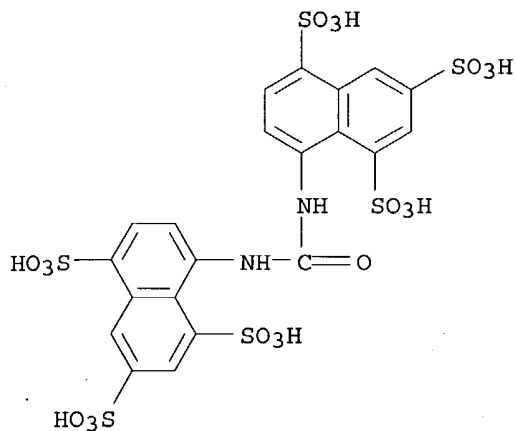
RN 104954-43-0 HCAPLUS

CN 2,7-Naphthalenedisulfonic acid, 4,4'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



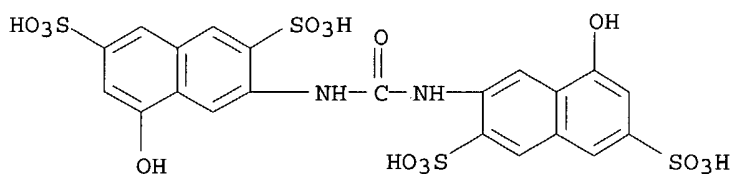
RN 104954-44-1 HCAPLUS

CN 1,3,5-Naphthalenetrisulfonic acid, 8,8'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



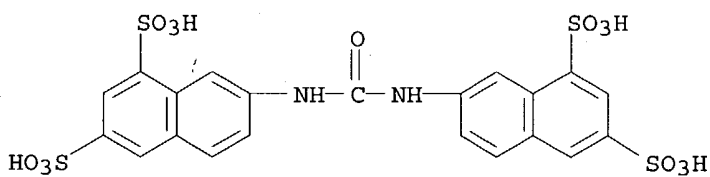
RN 104954-45-2 HCAPLUS

CN 2,7-Naphthalenedisulfonic acid, 3,3'-(carbonyldiimino)bis[5-hydroxy- (9CI)
(CA INDEX NAME)



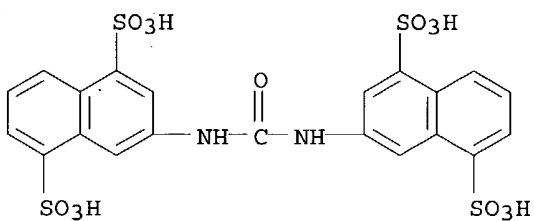
RN 157872-23-6 HCAPLUS

CN 1,3-Naphthalenedisulfonic acid, 7,7'-(carbonyldiimino)bis- (9CI) (CA
INDEX NAME)



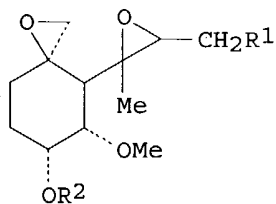
RN 158195-72-3 HCAPLUS

CN 1,5-Naphthalenedisulfonic acid, 3,3'-(carbonyldiimino)bis- (9CI) (CA
INDEX NAME)



DOCUMENT NUMBER: 113:152790
 TITLE: Preparation of O-acylfumagillols and analogs as angiogenesis inhibitors
 INVENTOR(S): Kishimoto, Shoji; Fujita, Takeshi; Kanamaru, Tsuneo; Folkman, Moses Judah; Ingber, Donald
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan; Children's Medical Center Corp.
 SOURCE: Eur. Pat. Appl., 50 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 357061	A1	19900307	EP 1989-116053	19890831
EP 357061	B1	19940608		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 03007222	A2	19910114	JP 1989-223064	19890831
JP 06060095	B4	19940810		
CA 1329771	A1	19940524	CA 1989-610069	19890831
AT 106726	E	19940615	AT 1989-116053	19890831
ES 2053890	T3	19940801	ES 1989-116053	19890831
KR 141692	B1	19980601	KR 1989-12555	19890831
US 5166172	A	19921124	US 1991-662120	19910228
US 5164410	A	19921117	US 1991-714436	19910613
US 5180738	A	19930119	US 1991-717876	19910613
US 5290807	A	19940301	US 1992-917827	19920721
US 5698586	A	19971216	US 1992-917842	19920721
JP 06256331	A2	19940913	JP 1993-298750	19931129
JP 2858724	B2	19990217		
PRIORITY APPLN. INFO.:			JP 1988-219287	A 19880901
			JP 1989-53537	A 19890306
			US 1989-391980	A 19890810
			US 1989-392028	B1 19890810
			EP 1989-116053	A 19890831
			US 1991-811800	B1 19911219
			US 1991-811880	B1 19911219
OTHER SOURCE(S):			MARPAT 113:152790	
GI				



I

AB The title compds. [I; R₁ = (un)substituted CH:CM₂, CH₂CHMe₂; R₂ = substituted alkanoyl, aroyl, (un)substituted heteroarylcarbonyl, CONH₂, alkyl, PhSO₂, alkylsulfonyl, H₂NSO₂, alkoxy carbonyl, PhO₂C] were prepared. Thus, fumagillol was stirred 2 h at 0° with ClCH₂CONCO in CH₂Cl₂ containing dimethylaminopyridine to give I (R₁ = CH:CM₂, R₂ = CONHCOCH₂Cl) which suppressed B16 mouse melanoma tumor growth to 20% that of controls after 3 wk in mice receiving 30 mg/kg s.c. every other day.

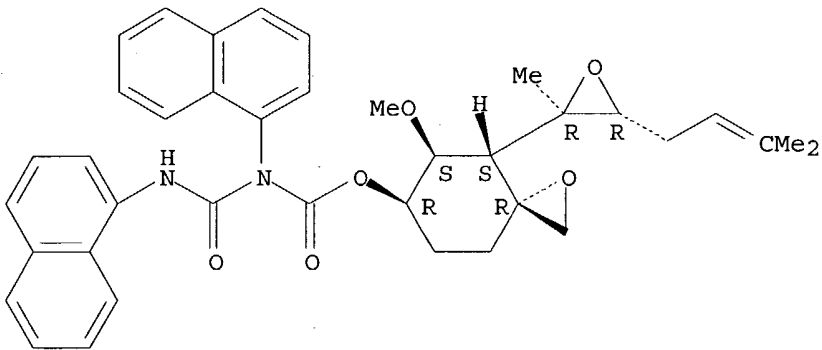
IT 129298-95-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as angiogenesis inhibitor)

RN 129298-95-9 HCAPLUS

CN Carbamic acid, 1-naphthalenyl[(1-naphthalenylamino)carbonyl]-,
(3R,4S,5S,6R)-5-methoxy-4-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L27 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1965:462596 HCAPLUS

DOCUMENT NUMBER: 63:62596

ORIGINAL REFERENCE NO.: 63:11395e-h

TITLE: Molecular properties and anticholinergic activity in compounds containing a tertiary amine group and a quaternary ammonium group

AUTHOR(S): Pratesi, P.; Villa, L.; Grana, E.; Lilla, L.

CORPORATE SOURCE: Univ. Pavia, Italy

SOURCE: Farmaco, Edizione Scientifica (1963), 18(1), 3-19
CODEN: FRPSAX; ISSN: 0430-0920

DOCUMENT TYPE: Journal

LANGUAGE: Italian

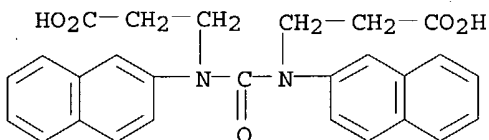
AB [RR1NCH2CH2N+R2R3R4]X- (I) are prepared Thus, 0.01 mole Ph2NCH2CH2NMe2 in alc. is treated at room temperature with 0.01 mole MeBr in alc. (25% solution) and the mixture is kept 48 hrs. to give trimethyl-β-diphenylaminoethylammonium bromide, m. 158-9° (98% alc.). Similarly prepared are the following I (R = R1 = Ph) (R2, R3, R4, X, and m.p. given): Et, Et, Et, Br, 172-3°; Me, iso-Pr, iso-Pr, Br, 200-1°; Me, (NR3R4 =) N-pyrrolidinyll, Br, 106-7°; Me, (NR3R4 =) morpholino, Br, 223-4°. Also prepared are the following I (R = Ph, R1 = cyclohexyl) (R2, R3, R4, X, and m.p. given): Me, Me, Me, Br, 179-80°; Et, Et, Et, Br, 145-6°; Me, iso-Pr, iso-Pr, I, 139-40°; Me, (NR3R4 =) N-pyrrolidinyll, I, 68-70°; Me, (NR3R4 =) morpholino, Br, 156-7°. Also prepared are the following I (R = R1 = cyclohexyl) (R2, R3, R4, X, and m.p. given): Et, Et, Et, Br, 161-2°; Me, (NR3R4 =) N-pyrrolidinyll, Br, 203-4°; Me, (NR3R4 =) morpholino, Br, 187-8°; Me, Me, Me, I, 174-5° (EtOH); Me, iso-Pr, iso-Pr, Br, 170-2° (EtOH). Also prepared are the following RR1MCH2CH2NR22 (II) (R = Ph, R1 = cyclohexyl) (R2 or NR22 and b.p./mm. given): Me, 158-9°/1; Et, 164-5°/0.8; iso-Pr, 178-80°/0.8; N-pyrrolidinyll, 194-5°/1.5; morpholino, 191-2°/0.6. Also prepared are the following II (R = R1 = cyclohexyl) (R2 or NR22 and b.p./mm. given): Et, 188-90°/20; N-pyrrolidinyll,

163-4°/0.6; morpholino, 190-1°. Also prepared are II (R = R1 = Ph, R2 = iso-Pr), b0.6 177°; β -iodoethyldicyclohexylamine-HI, m. 194-5° (EtOH). The anticholinergic activities for II decrease in the following order (NR2R3R4 given): N(Pr-iso)2Me, NEt3, N-methylpyrrolidine, NMe3. Among the I where NR2R3 = piperidino, R4 = Me, and R is cyclohexyl, cyclohexylmethyl, and PhCH2 and R1 is Ph, PhCH2, cyclohexyl, and cyclohexylmethyl, the cholinolytic activity decreases as the pKa decreases.

IT 3114-13-4, β -Alanine, N,N'-carbonylbis[N-2-naphthyl-
3114-14-5, β -Alanine, N,N'-carbonylbis[N-1-naphthyl-
(preparation of)

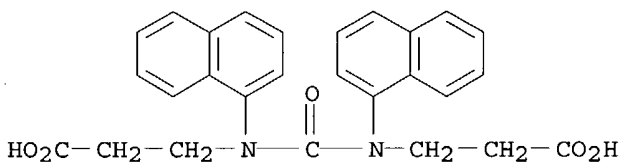
RN 3114-13-4 HCAPLUS

CN β -Alanine, N,N'-carbonylbis[N-2-naphthalenyl- (9CI) (CA INDEX NAME)



RN 3114-14-5 HCAPLUS

CN β -Alanine, N,N'-carbonylbis[N-1-naphthalenyl- (9CI) (CA INDEX NAME)



L27 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1957:62160 HCAPLUS

DOCUMENT NUMBER: 51:62160

ORIGINAL REFERENCE NO.: 51:11268b-i,11269a-i,11270a-f

TITLE: Preparation and bacteriostatic activity of substituted ureas

AUTHOR(S): Beaver, David J.; Roman, Daniel P.; Stoffel, Paul J.

CORPORATE SOURCE: Monsanto Chem. Co., St. Louis, MO

SOURCE: Journal of the American Chemical Society (1957), 79, 1236-45

CODEN: JACSAT; ISSN: 0002-7863

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

AB cf. C.A. 49, 924b. The preparation and in vitro bacteriostatic activity of some ureas, carbanilides, and related compds. against *Micrococcus pyrogenes* var. *aureus* are described. The bacteriostatic properties of ureas were remarkably specific in that activity was greatly enhanced or completely lost with slight changes in chemical structure. Activity is drastically reduced by o-substitution regardless of the electronic character of the substituent. Thioureas were invariably less effective than similarly substituted ureas. Bromocarbanilides were less active than the Cl compds. in both ureas and thioureas. Procedure A: PhNCO (11.9 g.) in 50 cc. Et2O added dropwise to 16.2 g. 3,4-Cl2C6H3NH2 (I) in 50 cc. Et2O, the mixture held 2 hrs., and filtered yielded 3,4-dichlorocarbanilide. In the subprocedures the following solvents were used: A2, Skellysolve; A3, C6H6; A4, Me2CO; A5, absolute EtOH; A6, none; A7, none, 4 hrs. at 90°. Procedure B: 3,4-Cl2C6H3NCS (20.4 g.) and 16.2 g. I in 75 cc.

absolute EtOH refluxed 1 hr. yielded 3,3',4,4'-tetrachlorothiocarbanilide. Procedure C: PhNCO (11.9 g.) in 400 cc. Et₂O at 20° treated with anhydrous NH₃ yielded phenylurea. Procedure D: 2-C₁₀H₇NH₂ (60.0 g.) and 24.0 g. urea heated to 160° and held there 3 hrs. yielded 1,3-di-2-naphthylurea. Procedure E: Cyclohexylamine (60.0 g.) in 800 cc. PhMe treated at 100° with COCl₂ yielded 1,3-dicyclohexylurea. For compds. of the type RNHC(:X)NHR', R, X, R', procedure, % yield, and m.p. are: H, O, 2-C₁₀H₇, C, 96.8, 212° (decomposition); H, O, 4-biphenyl, C, 97.0, 209° (decomposition); 1-C₁₀H₇, O, 1-C₁₀H₇, D, 49.8, 295-6°; 2-C₁₀H₇, O, 2-C₁₀H₇, D, 86.7, 305-6°; 2-C₁₀H₇, O, CH₂CH₂CH₂OMe, A, 80.0, 142.5-3.0°; 1-C₁₀H₇, O, cyclohexyl, A, 100.0, 237.0-8.0°; 2-C₁₀H₇, O, dicyclohexyl, A, 99.3, 177.3-7.8°; cyclohexyl, O, cyclohexyl, E, 30.2, 226.0-7.0°; dicyclohexyl, O, Et, A, 87.4, 146.8-7.5°; dicyclohexyl, O, dicyclohexyl, E, 36.5, 81.0-1.7°; cyclohexyl, S, Ph, A5, 91.5, 150.1-50.9°; cyclohexyl, S, 4-C₆H₄OEt, B, 74.5, 122.2-3.0°; cyclohexyl, S, 4-Me₂NC₆H₄, B, 91.0, 127.0-7.8°; cyclohexyl, S, 1-C₁₀H₇, B, 74.2, 141.8-2.5°; cyclohexyl, S, dicyclohexyl, B, 49.2, 103.2-3.6°; Ph, S, 4-Me₂NC₆H₄, B, 84.2, 154.4-4.8°; Ph, S, 2-C₁₀H₇, B, 83.6, 158.2-9.0°; Ph, S, dicyclohexyl, B, 63.7, 86.5-7.3°; Ph, S, 4-C₆H₄OEt, A5, 89.8, 133.9-4.3°; 3,4-Br₂C₆H₃, S, 4-BrC₆H₄, A7, 47.5, 125.0-6.1°. For RC₆H₄NHCONR₁R₂, R, R₁, R₂, procedure, % yield, and m.p. are: H, H, H, C, 61.5, 148.5-9.0°; H, H, CH₂CH₂CH₂NEt₂, A6, 100, 69.5-70.0°; H, H, CH₂CH₂CH₂NHCHMe₂, A2, 58.0, 143.7-4.2°; H, H, CH₂CH₂CH₂OMe, A7, 100.0, 87.5-8.2°; H, H, cyclohexyl, A7, 97.3, 186.3-7.1°; H, H, 2-C₁₀H₇, A5, 73.3, 233.0-4.0°; H, cyclohexyl, cyclohexyl, A, 79.4, 180.3-1.3°; H, allyl, allyl, A2, 100.0, 65.5-6.0°; H, PhNHCONHCH₂CH₂CH₂, PhNHCONHCH₂CH₂CH₂, A6, 100, 132° (decomposition); H, Bu, Bu, A6, 98.6, 82.7-3.0°; H, heptyl, heptyl, A, 76.0, -; H, 2-ethylhexyl, 2-ethylhexyl, A7, 93.7, -; H, Ph, Ph, A7, 86.8, 136.0-6.6°; 2-Me, H, cyclohexyl, A, 95.1, 196.1-6.5°; 2-Me, cyclohexyl, cyclohexyl, A, 86.0, 142.2-2.8°; 4-Me, H, cyclohexyl, A, 100.0, 205.2-5.8°; 4-Me, cyclohexyl, cyclohexyl, A, 91.5, 173.4-3.7°; 2-MeO, cyclohexyl, cyclohexyl, A, 100.0, 155.3-6.0°; 2-EtO, H, CH₂CH₂CH₂OMe, A6, 78.0, 86.6-7.2°; 2-EtO, H, 2-C₁₀H₇, A, 71.0, 177.5-8.2°; 2-EtO, cyclohexyl, cyclohexyl, A, 65.2, 99.8-100.4°; 4-EtO, H, Et, A, 85.3, 151.9-2.4°; 4-EtO, H, 1-C₁₀H₇, A, 97.6, 238.0-9.0°; 4-EtO, H, 2-C₁₀H₇, A, 99.3, 237.4-8.0°; 4-EtO, H, cyclohexyl, A, 95.6, 182.6-3.0°; 4-EtO, cyclohexyl, cyclohexyl, A, 91.8, 149.6-50.2°; dodecyl, cyclohexyl, cyclohexyl, A2, 100.0, -; 4-Me₂N, 1-C₁₀H₇, H, A, 96.0, 227.5-8.5°; 4-Me₂N, 2-C₁₀H₇, H, A, 91.3, 252-3°; 2-Ph, H, Et, A, 88.0, 114.6-15.2°; 2-Ph, cyclohexyl, cyclohexyl, A, 100, 110.0-10.7°; 2-Ph, H, CH₂CH₂CH₂NEt₂, A6, 100.0, 76.4-7.0°; 4-Cl, formyl, 2,4-Cl₂C₆H₃, A7, 85.3, 118.5-19.1°; 4-Cl, formyl, 3,4-Cl₂C₆H₃, A7, 63.0, 122.5-3.5°; 4-Cl, allyl, 3,4-Cl₂C₆H₃, A2, 87.2, 151.2-2.0°; 2-MeO, formyl, 2,5-Cl₂C₆H₃, A7, 71.0, 152.5-3.0°. For compds. of the type RC₆H₄NHCONHC₆H₄R', R, R' (all procedure A except as noted), % yield, and m.p. are: H, 2-MeO, 84.3, 146.2-6.8°; H, 2-EtO, 94.4, 173.8-4.2°; H, 4-EtO, 100.0, 188.2-8.8°; H, 2-Et, 61.2, 184.9-5.5°; H, 4-Me₂N, 94.0, 208.0-8.8°; H, 4-Et₂N, 88.8, 178.7-9.3°; H, 2-Ph, 95.7, 173.0-3.6°; H, 4-Ph, 85.5, 240-1°; H, 4-H₂N, 78.5, above 400°; H, 4-PhNH, 98.2, 212.8-13.8°; H, 4-Cl, 95.0, 250-1°; 2-MeO, 2,4-Cl₂, 99.5, 222.3-3.0°; 4-MeO, 2,4-Cl₂, 58.0, 230.0-30.5°; 2-EtO, 4-EtO, 65.2, 146.4-7.0°; 4-EtO, 2-Me, 84.0, 202.0-2.4°; 4-EtO, 4-Me, 100.0, 220.4-1.0°; 4-EtO, 4-Me₂N, 91.1, 211.8-12.2°; 4-EtO, dodecyl, A2, 100.0, -; 4-EtO, 2-Ph, 95.8, 194.8-5.4°; 2-Ph, 4-PhNH, 86.8, 155.8-6.2°; 2-Ph, 2-Ph, 74.0, 182.2-2.8°; 4-Ph, 4-Ph, 76.5,

312° (decomposition); 4-Cl, 4-Cl, 98.0, 315-19°; 4-Cl, 2,4-Cl₂, 98.0, 253.0-3.8°; 4-Cl, 2,5-Cl₂, 83.0, 261.5-2.5°; 3-Cl, 3,4-Br₂, 94.0, 208-5-9.0°; 2,4-Cl₂, 2,4-Cl₂, 97.5, 261-3°.

For 3,4-Cl₂C₆H₃NHCONRR', R, R' (all procedure A except as noted), % yield, and m.p. are: H, H, C, 93.7, 155.6-6.3°; H, Et, 100.0, 179.5-80.1°; H, tert-octyl, 100.0, 145.8.6°; H, cyclohexyl, 100.0, 188.0-8.7°; H, 1-Cl₁₀H₇, 97.0, 265-6°; H, 2-Cl₁₀H₇, 97.2, 267-8°; H, CH₂CH(OH)Me, 100, 152.0-2.8°; H, CH₂CH₂CH₂OH, 98.8, 126.5-8.0°; H, tetrahydrofurfuryl, 100.0, 144.1-4.9°; Et, 4-ClC₆H₄, 77.0, 116.0-6.8°; allyl, allyl, A₂, 100.0, 62.5-3.5°; allyl, iso-Pr, 93.4, 84.0-4.5°; CH₂CH₂OH, CH₂CH₂OH, 65.0, 156.8-7.6°; CH₂:CClCH₂, CH₂:CClCH₂, 100, 100.7-1.4°; CH₂:CClCH₂, iso-Pr, 100, 84.7-5.2; CH₂:CClCH₂, tert-Bu, 100.0, 93.9-5.0°; CHCl:CHCH₂, CHCl:CHCH₂, 100.0, 156.0-6.6°; CH₂:CClCH₂, CH₂CH₂CH₂OMe, A₂, 100, -; CH₂:CClCH₂, Ph, A₇, 92.9, 118.7-9.4°; H, CHCl:CClCH₂, 61.2, 105.1-5.9°; Bu, Ph, 96.5, 98.5-9.4°; CH₂CH₂CN, Ph, 89.3, 114.7-15.5°; iso-Pr, MeC.tplbond.C, 71.1, 84.4-5.1°; Ph, Ph, 39.5, 148.3-9.1°; cyclohexyl, cyclohexyl, 98.0, 177.6-8.4°; cyclohexyl, MeCH:CClCH₂, 88.7, 160.4-60.8°; allyl, 4-C₆H₄OEt, 100, -; allyl, 3,4-Cl₂C₆H₃, A₂, 87.3, 116.8-17.5°; MeC.tplbond.C, 3,4-Cl₂C₆H₃, 69.0, 145.2-6.0°; Bu, Ph, 96.5, 98.5-9.4°; H, 2-thiazolyl, A₄, 99.0, 225° (decomposition). For 3,4-Cl₂C₆H₃NHCONHC₆H₄R, R, procedure (A unless otherwise noted), % yield, and m.p. are: H, 100, 217.2-7.7°; 4-Me, 100.0, 258.0-9.0°; 2-MeO, 95.2, 173.8-4.3°; 4-MeO, 93.5, 233.1-4.0°; 4-Me₂N, 95.0, 229.6-30.4°; 4-H₂N, A₃, 96.0, above 360°; dodecyl, A₇, 98.0, -; 2-Ph, 91.6, 183.3-4.1; 4-Ph, 84.5, 233.0-4.0°; 2-Cl, 87.0, 220.0-20.6°; 3-Cl, 91.5, 210.7-11.3°; 4-Cl, 88.0, 255.2-56.2°; 2,4-Cl₂, 97.3, 238.5-9.2°; 2,5-Cl₂, 94.2, 242.2-2.6°; 3,4-Cl₂, 100.0, 281-2°; 3,4,5-Cl₃, 100.0, 308-10°; 3-Cl-4-HO, 95.4, 237.4-8.0°; 3,5-Cl₂-4-HO, 92.4, 272-3°; 3-Br, 100.0, 208.5-9.2°; 4-PhNH, 100, 208.8-9.5°; 4-HO, A₃, 82.5, 213.8-14.5°; 4-NO₂, 95.3, 294-5°; 4-sulfamyl, A₄, 83.6, 258.5-9.5°; 4-(2-thiazolesulfamyl), A₄, 82.8, 271-2°; 4-(2-pyrimidinesulfamyl), A₄, 79.0, 290° (decomposition). For RC₆H₄NHC:XR', R, X, R', procedure, % yield, and m.p. are; H, O, morpholino, A, 74.5, 159.3-60.0°; H, S, morpholino, B, 72.6, 132.6-3.4°; H, O, 2-methyl-1-piperidyl, A, 94.5, 115.4-16.0°; H, O, 1,2-dihydro-2,2,4-trimethyl-1-quinolyl, A, 71.0, 125.5-6.2°; H, O, 1,2-dihydro-6-ethoxy-2,2,4-trimethyl-1-quinolyl, A, 94.2, 146.6-7.0°; H, O, 1,2-dihydro-6-phenyl-2,2,4-trimethyl-1-quinolyl, A, 40.5, 148.0-9.1°; 4-MeO, O, morpholino, A₂, 95.7, 124.5-5.0°; 2-Cl, O, morpholino, A₂, 93.8, 132.2-2.8°; 3-Cl, O, morpholino, A₂, 98.3, 129.7-30.3°; 4-Cl, O, 4-morpholino, A₂, 91.4, 200.8-1.4°; 3,4-Cl₂, O, morpholino, A, 90.0, 157.1-7.8°; 3,4-Cl₂, S, morpholino, B, 96.8, 197.5-8.1°; 3,4-Cl₂, O, 1-piperidyl, A, 100.0, 175.0-5.8°; 3,4-Cl₂, O, 2-methyl-1-piperidyl, A₂, 97.5, 171.4-1.9°; 3,4-Cl₂, O, 3-methyl-1-piperidyl, A, 56.5, 115.7-6.7°; 3,4-Cl₂, O, 4-methyl-1-piperidyl, A₂, 92.5, 144.0-4.8°; 3,4-Cl₂, O, 1-pyrrolidyl, A, 97.8, 176.8-7.4°; 3,4-Cl₂, O, 2-pyrrolidon-1-yl, A, 89.3, 151.8-2.7°; 3,4-Cl₂, O, 3,4-Cl₂, 2-thiono-1-pyridyl, A₄, 90.5, 171.9-2.8°; 3,4-Cl₂, S, 2-thiono-1-pyrrolidyl, A₇, 52.6, 126.7-7.2°; 3,4-Cl₂, O, 3-methylpyrazin-5-on-1-yl, A₄, 62.3, 228.0-9.0°; 3,4-Cl₂, O, 2,4,6-trimethyl-1-piperidyl, A, 85.5, 135.3-6.1°; 3,4-Cl₂, O, 1-decahydroquinolyl, A, 99.7, 160.5-1.4°; 3,4-Cl₂, O, 2-decahydroisoquinolyl, A, 90.4, 144.0-5.0°; 3,4-Cl₂, O, 1,2-dihydro-6-ethoxy-2,2,4-trimethyl-1-quinolyl, A, 54.0, 139.3-40.2°. For 3,4-Cl₂C₆H₃NHCSNRR', R, R', procedure, % yield, and m.p. are: H, CH₂CH₂CH₂OH, A₂, 99.0, 34-5°; H, 4-ClC₆H₄, B, 82.0, 154.2-4.9°; H, 3-ClC₆H₄, B, 75.5,

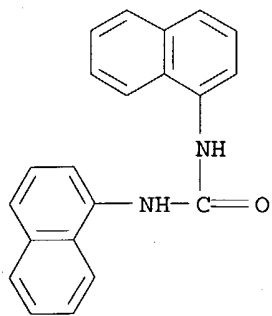
119.5-20.5°; H, Ph, B, 99.0, 136.1-7.0°; H, 3-BrC₆H₆, A7, 74.6, 107.5-8.3°; H, 3,4-Cl₂C₆H₃, B, 94.5, 162.6-3.5°; H, 2-thenyl, A, 99.0, 153.2-4.1°; iso-Pr, allyl, A2, 93.4, 80.8-1.6°; iso-Pr, MeC.tplbond.C, A2, 88.7, 77.2-7.8°.

Procedures are given for new compds. 3,4-Cl₂C₆H₃XC₆H₄R, for which X, R, % yield, and m.p. follow: CONH, 3,4-d-Cl₂, 86.5, 232.6-3.3°; CSNH, 4-Cl, 77.0, 144.5-5.3°; CONH, 4-Cl, 80.0, 167.3-8.1°; CH₂NH, 4-Cl, 18.5, 169.0-0.5°; NHCH₂, 4-Cl, 18.0, 122.3-3.1°; NHCO, 4-Cl, 73.3, 176.6-7.4°; N:CH, 3,4-Cl₂, 86.5, 132.3-3.0°; N:CH, 4-Cl, 81.0, 103.7-4.4°; NHCH₂CO, 4-Cl, 80.0, 182.5-3.7°; NHCOCH₂CONH, 3,4-Cl₂, 28.7, 227.8-8.6; CH:CHCOCH:CH, 3,4-Cl₂, 59.3, 202.1-2.8°; NHCOCONH, 3,4-Cl₂, 27.3, 228.2-9.1°; NHC(:NH)NH, 3,4-Cl₂, 74.0, 181.1-2.0°; NHCOCH:CHCONH, 3,4-Cl₂, 85.0, 227-9°; NHCO₂CH₂CH₂OCONH, 3,4-Cl₂, 79.3, 217.3-18.0°; NHCONH(CH₂)₄NHCONH, 3,4-Cl₂, 100.0, 197.2-8.2°; NHCOC₆H₄ CONH-o, 3,4-Cl₂, 71.8, 256-7°; NHCONHC₆H₄NHCONH-p, 3,4-Cl₂, 94.3, above 360°; NHCONHCH₂, 3,4-Cl₂, 90.0, 194.7-5.8°; CH₂NHCONH, 4-Cl, 88.8, 213.2-13.7°; NHCO₂C₆H₄O₂CNH-p, 3,4-Cl₂, 84.5, 279-80°; NHSONH, 3,4-Cl₂, 70.6, 49.5-50.2°; NHCO₂CH₂CH₂SCH₂CH₂OCONH, 3,4-Cl₂, 87.3, 141.4-2.5°; CONHCONHCO, 3,4-Cl₂, 70.0, 199.6-200.4°; NHCSNHNHCSNH, 3,4-Cl₂, 89.9, 169° (decomposition); NHCONHNHCONH, 3,4-Cl₂, 88.8, 233-4°; NHCONHNH, H, 97.8, 172.2-3.1°; NHCO₂(CH₂)₄OCONH, 3,4-Cl₂, 86.0, 170.9-1.8°; CCl₃CH:, 3,4-Cl₂, 74.9, 101.3-2.1°; NHCH:N, 3,4-Cl₂, 73.0, 158.3-9.1°; NHCO₂, 4-Cl, 88.8, 149.5-50.7°; NHCO₂, 3,4-Cl, 91.5, 148.1-9.1°. I (162.1 g.) at 75-80° treated dropwise with 60.0 g. MeC.tplbond.CBr, the slurry held 3 hrs. at 85°, cooled, neutralized at 20° (ice bath) with 30 g. NaOH in 500 cc. H₂O, the oil extracted with Et₂O, and the extract fractionated yielded N-(2-propynyl)-3,4-dichloroaniline, b7 152.7-3.4°, n_D25 1.5991. I treated with CH₂:CHCH₂Cl and the product held 18 hrs. at 80-5° yielded N-allyl-3,4-dichloroaniline, b7.5 159.0-61.0, n_D25 1.5859. EtOAc (1 l.) saturated with COCl₂, treated at reflux during 2-3 hrs. with 324 g. I in 1.5 l. EtOAc under a flow of COCl₂, the solution held 1 hr. at reflux, 1.5 l. EtOAc distilled at atmospheric pressure, and the remaining EtOAc removed under a gradually increasing vacuum yielded 90.5% 3,4-dichlorophenyl isocyanate, b10.5 116.7-18.1°, m. 40-1°. H₂O (350 cc) containing 58.0 cc. 38% HCl treated during 30 min. at 10-15° with 80.0 g. CSCl₂, the cooling bath removed, 128.0 g. I in 400 cc. PhMe added during 30-60 min., the product held 3 hrs. at 85°, filtered, and the PhMe layer separated and fractionated yielded 95.1% 3,4-dichlorophenyl isothiocyanate, b7.0 134.8-5.9°. 3,4-Br₂C₆H₃NH₂ by the same method yielded 86.5% crude 3,4-dibromophenyl isothiocyanate.

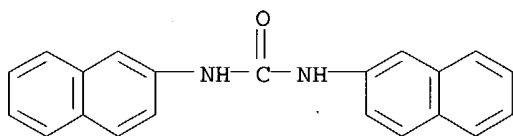
IT 607-56-7, Urea, 1,3-di-1-naphthyl- 33102-63-5, Urea, 1,3-di-2-naphthyl- (and their bacteriostatic activity)

RN 607-56-7 HCAPLUS

CN Urea, N,N'-di-1-naphthalenyl- (9CI) (CA INDEX NAME)



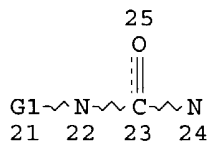
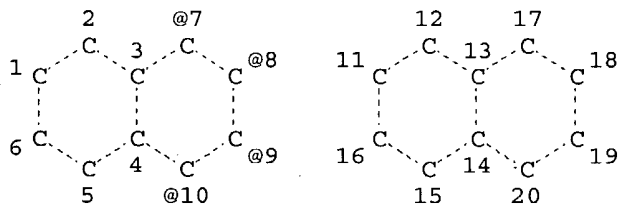
RN 33102-63-5 HCAPLUS
 CN Urea, N,N'-di-2-naphthalenyl- (9CI) (CA INDEX NAME)



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L1 STR



VAR G1=7/8/9/10

NODE ATTRIBUTES:

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DEFAULT ECLEVEL IS LIMITED

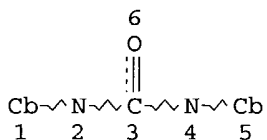
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STEREO ATTRIBUTES: NONE

L3 STR



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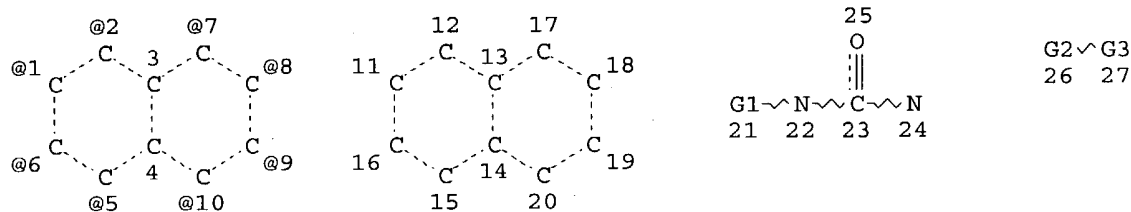
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GGCAT IS PCY AT 5
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GRAPH ATTRIBUTES:
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 NUMBER OF NODES IS 6

STEREO ATTRIBUTES: NONE

L8 906 SEA FILE=REGISTRY SSS FUL L1 AND L3
 L9 STR



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 @28 29 @30 31 32 @33 34 35 @36 37 @38 39

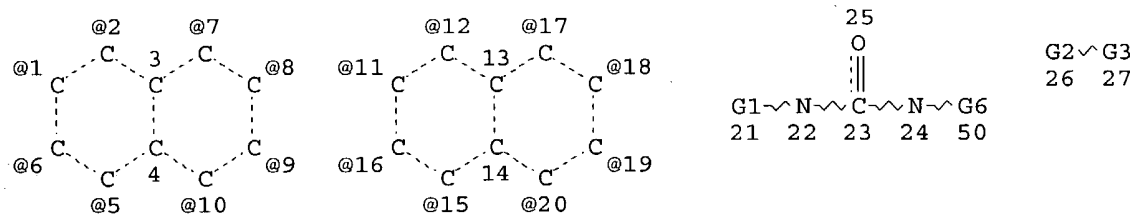
O~C=O SO2~N O=C~N
 40 @41 42 @43 44 45 @46 47

VAR G1=7/8/9/10
 VAR G2=1/2/5/6
 VAR G3=28/30/33/36/38/41/43/46
 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE

L10 200 SEA FILE=REGISTRY SUB=L8 SSS FUL L9
 L12 STR



N~SO2 N~C=O SO2~O O=C~O O~SO2
 @28 29 @30 31 32 @33 34 35 @36 37 @38 39

O~C=O SO2~N O=C~N G4~G5
 40 @41 42 @43 44 45 @46 47 48 49

VAR G1=7/8/9/10
 VAR G2=1/2/5/6
 VAR G3=28/30/33/36/38/41/43/46
 VAR G4=17/18/19/20
 VAR G5=28/30/33/36/38/41/43/46
 VAR G6=11/12/15/16

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 50

STEREO ATTRIBUTES: NONE

L14 68 SEA FILE=REGISTRY SUB=L8 SSS FUL L12
 L15 69 SEA FILE=HCAPLUS ABB=ON PLU=ON L14
 L17 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 AND (?MEDI? OR ?THERAP?
 OR ?DRUG? OR ?PHARMA?)
 L18 62 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 NOT L17
 L20 STR

N==N

1 2

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 2

STEREO ATTRIBUTES: NONE

L22 277 SEA FILE=REGISTRY SUB=L8 SSS FUL L1 NOT L20
 L23 265 SEA FILE=REGISTRY ABB=ON PLU=ON L22 NOT L10
 L24 223 SEA FILE=HCAPLUS ABB=ON PLU=ON L23
 L26 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND (?MEDIC? OR ?THERAP?
 OR ?DRUG? OR ?PHARMA?)
 L27 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L26 NOT (L17 OR L18)
 L31 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 (L) (?INSUL? OR ?GLYCEM? OR
 ?DIABET? OR ?ACIDOS? OR ?DYSTROP? OR ?GLYCERIDEM?)
 L32 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND (HIV OR ?PROTEAS? OR
 ?PROTEINA? OR ?IMMUNODEF?)
 L33 4 SEA FILE=HCAPLUS ABB=ON PLU=ON (L31 OR L32) NOT (L17 OR L18
 OR L27)

=>

=>

=> d ibib abs hitstr l33 1-4

L33 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:433797 HCAPLUS

DOCUMENT NUMBER: 140:423477

TITLE: Preparation of diaryl ureas as inhibitors of p38
kinase

INVENTOR(S): Miller, Scott; Osterhout, Martin; Dumas, Jacques;
 Khire, Uday; Lowinger, Timothy B.; Scott, William J.;
 Smith, Roger A.; Wood, Jill E.; Gunn, David E.;
 Hatoum-Mokdad, Holia; Rodriguez, Marell; Sibley,

Robert; Wang, Ming; Turner, Tiffany; Brennan,
Catherine

PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 60 pp., Cont. of U.S. Ser. No.
458,015, abandoned.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004102636	A1	20040527	US 2002-60396	20020201
PRIORITY APPLN. INFO.:			US 1997-126439P	P 19971222
			US 1998-285522	B1 19981222
			US 1999-458015	B1 19991210

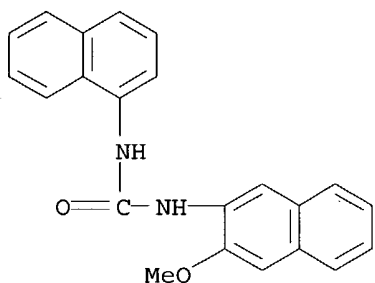
OTHER SOURCE(S): MARPAT 140:423477

AB A method of treating a p-38 mediated disease other than cancer comprises administration of BNHCONHA [A = (substituted) Ph, pyridyl, 2-thienyl; B = (substituted) aryl, heteroaryl containing ≥ 1 6-membered aromatic structure containing 0-4 N, O, or S atoms]. Thus, 5-tert-butyl-2-(3-tetrahydrofuranyloxy)aniline (preparation given) and p-tolyl isocyanate were stirred 8 h in PhMe to give 75% N-(5-tert-butyl-2-(3-tetrahydrofuranyloxy)phenyl)-N'-(4-methylphenyl)urea. Title compds. inhibited p38 kinase with IC₅₀ = 1-10 μ M.

IT 228400-96-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diaryl ureas as inhibitors of p38 kinase)

RN 228400-96-2 HCAPLUS

CN Urea, N-(3-methoxy-2-naphthalenyl)-N'-1-naphthalenyl- (9CI) (CA INDEX NAME)



L33 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:862665 HCAPLUS

DOCUMENT NUMBER: 138:163274

TITLE: Regulation of Insulin Receptor Function by a Small Molecule Insulin Receptor Activator

AUTHOR(S): Pender, Celia; Goldfine, Ira D.; Mancham, Vara Prasad; Evans, Joseph L.; Spevak, Wayne R.; Shi, Songyuan; Rao, Sandhya; Bajjalieh, Sonia; Maddux, Betty A.; Youngren, Jack F.

CORPORATE SOURCE: University of California, Mount Zion Medical Center, San Francisco, CA, 94143-1616, USA

SOURCE: Journal of Biological Chemistry (2002), 277(46), 43565-43571

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In type 2 diabetes mellitus, impaired insulin signaling leads to hyperglycemia and other metabolic abnormalities. TLK19780, a non-peptide small mol., is a new member of a novel class of anti-diabetic agents that function as activators of the insulin receptor (IR) β -subunit tyrosine kinase. In HTC-IR cells, 20 μ M TLK19780 enhanced maximal insulin-stimulated IR autophosphorylation 2-fold and increased insulin sensitivity 2-3-fold. In contrast, TLK19780 did not potentiate the action of insulin-like growth factor-1, indicating the selectivity of TLK19780 toward the IR. The predominant effect of TLK19780 was to increase the number of IR that underwent autophosphorylation. Kinetic studies indicated that TLK19780 acted very rapidly, with a maximal effect observed 2 min after addition to insulin-stimulated cells. In 3T3-L1 adipocytes, 5 μ M TLK19780 enhanced insulin-stimulated glucose transport, increasing both the sensitivity and maximal responsiveness to insulin. These studies indicate that at low micromolar levels small IR activator mols. can enhance insulin action in various cultured cells and suggest that this effect is mediated by increasing the number of IR that are tyrosine-phosphorylated in response to insulin. These studies suggest that these types of mols. could be developed to treat type 2 diabetes and other clin. conditions associated with insulin resistance.

IT 309932-59-0, TLK 19780

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

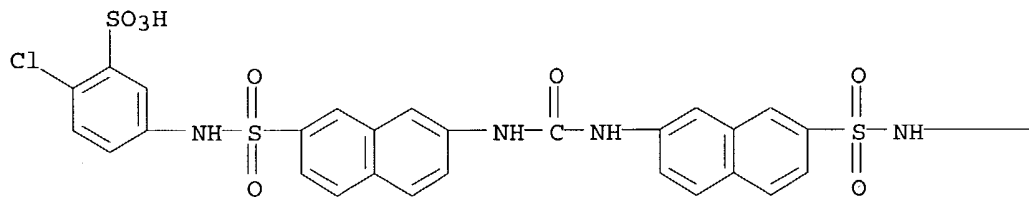
(regulation of **insulin** receptor function by a small mol.

insulin receptor activator TLK19780 via an increase in IR tyrosine phosphorylation)

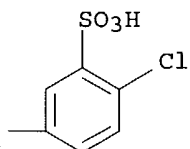
RN 309932-59-0 HCAPLUS

CN Benzenesulfonic acid, 3,3'-[carbonylbis(imino-7,2-naphthalenediylsulfonylimino)]bis[6-chloro- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:794315 HCAPLUS

DOCUMENT NUMBER: 137:289023
 TITLE: Method for determining whether a compound is an insulin receptor kinase activator
 INVENTOR(S): Mancham, Prasad V. V. S. V.; Lum, Robert T.; Schow, Steven R.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 6 pp., Cont.-in-part of U. S. Ser. No. 977,059.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

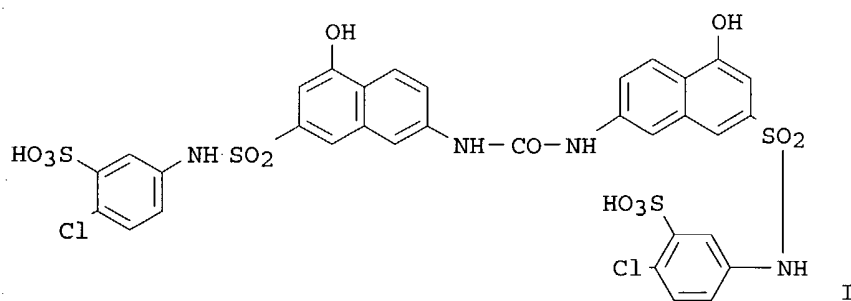
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002151542	A1	20021017	US 2002-115595	20020402
US 6528037	B2	20030304		
US 2002061927	A1	20020523	US 2001-977059	20011011
WO 2003085127	A2	20031016	WO 2003-US9805	20030331
WO 2003085127	A3	20040108		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
 US 2000-239636P P 20001011
 US 2001-977059 A2 20011011
 US 2002-115595 A 20020402

GI



AB A method is provided for determining whether a compound is an insulin receptor kinase activator. The methodol. of the invention comprises administering the compound to a non-human mammal concurrently treated with an **HIV protease** inhibitor; administering glucose to the mammal; and measuring the level of plasma insulin or plasma glucose in the mammal, where a reduced level of plasma insulin or plasma glucose in the mammal compared to a comparable mammal that has been treated with the **HIV protease** inhibitor and administered the glucose, but not administered the compound, indicates that the compound is an insulin receptor

kinase activator. Reversal of **protease** inhibitor-mediated insulin resistance in normal rats by I (preparation included) is described.

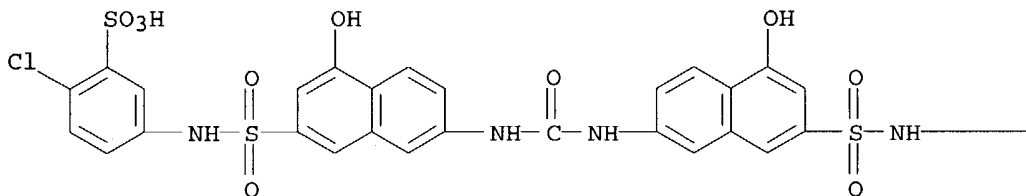
IT 309932-60-3P

RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**insulin** receptor kinase activator determination)

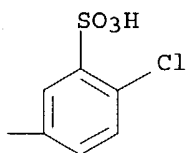
RN 309932-60-3 HCAPLUS

CN Benzenesulfonic acid, 3,3'-[carbonylbis[imino(4-hydroxy-7,2-naphthalenediyl)sulfonylimino]]bis[6-chloro- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

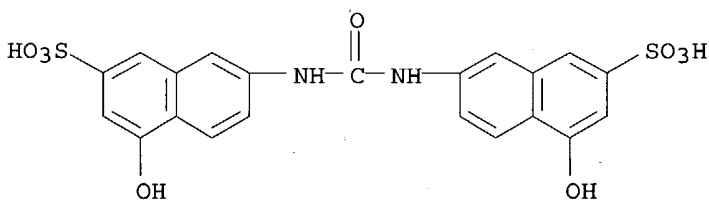


IT 20324-87-2P 309933-11-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; **insulin** receptor kinase activator determination)

RN 20324-87-2 HCAPLUS

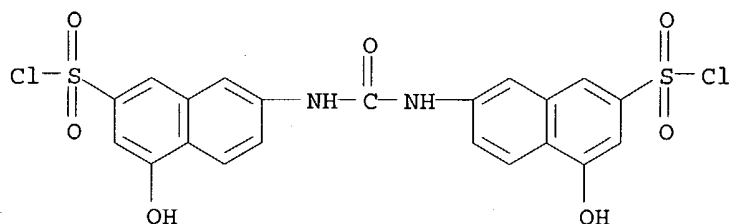
CN 2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis[4-hydroxy-, disodium salt (9CI) (CA INDEX NAME)



●2 Na

RN 309933-11-7 HCAPLUS

CN 2-Naphthalenesulfonyl chloride, 7,7'-(carbonyldiimino)bis[4-hydroxy- (9CI) (CA INDEX NAME)



L33 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:745021 HCAPLUS

DOCUMENT NUMBER: 130:13851

TITLE: Preparation of N,N'-bis(hydroxysulfonaphthyl)ureas and analogs as HIV reverse transcriptase and integrase inhibitors

INVENTOR(S): Kenyon, George L.; Stauber, Margaret J.; Maurer, Karl; Eargle, Dolan; Muscate, Angelika; Leavitt, Andrew; Roe, Diana C.; Ewing, Todd J. A.; Skillman, Allan G., Jr.; Arnold, Edward; Kuntz, Irwin D.; Young, Malin

PATENT ASSIGNEE(S): The Regents of the University of California, USA

SOURCE: PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

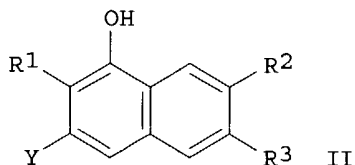
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9850347	A1	19981112	WO 1998-US8815	19980504
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9872735	A1	19981127	AU 1998-72735	19980504
US 6140368	A	20001031	US 1998-72484	19980504
PRIORITY APPLN. INFO.:			US 1997-45583P	P 19970505
			US 1998-72484	A 19980504
			WO 1998-US8815	W 19980504

OTHER SOURCE(S): MARPAT 130:13851

GI



AB RXR [I; R = hydroxynaphthyl group II; R1 substituents may be the same or different and = (un)substituted aryl or (un)substituted heteroaryl bound via an azo or amide group (sic); 1 of R2,R3 = H and the other = bond; Y

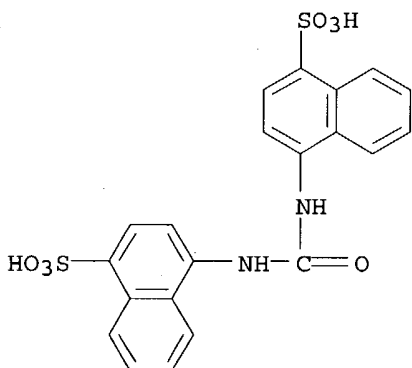
substituents may be the same or different and = sulfonic, carboxylic, tetrazol, or esters thereof (sic); X is a substantially rigid linker bonded via amide or amide analogous bonds (sic)] were prepared Thus, pyridine-2,6-dicarboxylic acid was bisamidated by 7-amino-4-hydroxynaphthalene-2-sulfonic acid and the product coupled with the diazonium salt prepared from 4-(H₂N)C₆H₄CO₂H to give RNHCOZCONHR [R = hydroxynaphthyl group II, R₁ = N:NC₆H₄(CO₂H)-4, R₂ = H, R₃ = bond, Y = SO₂H, Z = pyridine-2,6-diyl] monosodium salt. Data for biol. activity of I were given.

IT 5690-13-1 6266-54-2 115058-21-4
 157872-23-6 207974-37-6 207974-38-7
 207974-39-8 207974-40-1 207974-41-2
 207974-43-4 215785-49-2 215785-50-5
 215786-14-4 215786-15-5

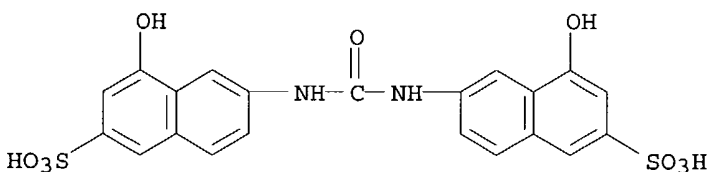
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(preparation of N,N'-bis(hydroxysulfonaphthyl)ureas and analogs as HIV reverse transcriptase and integrase inhibitors)

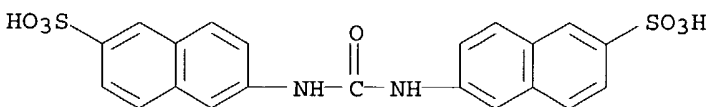
RN 5690-13-1 HCAPLUS
 CN 1-Naphthalenesulfonic acid, 4,4'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



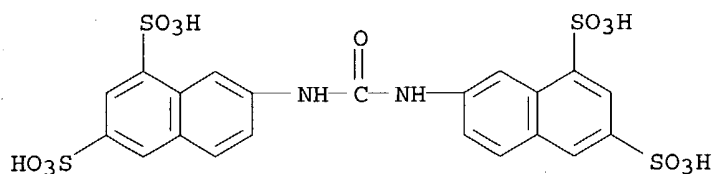
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 CN 2-Naphthalenesulfonic acid, 6,6'-(carbonyldiimino)bis[4-hydroxy- (9CI) (CA INDEX NAME)



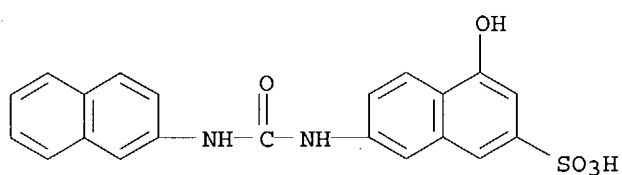
RN 115058-21-4 HCAPLUS
 CN 2-Naphthalenesulfonic acid, 6,6'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



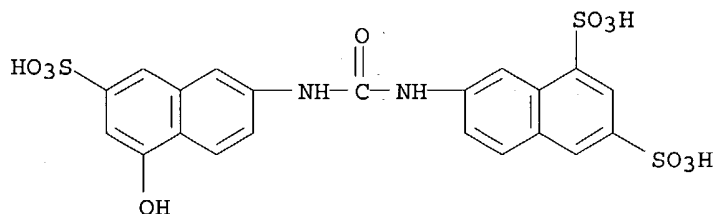
RN 157872-23-6 HCAPLUS
 CN 1,3-Naphthalenedisulfonic acid, 7,7'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



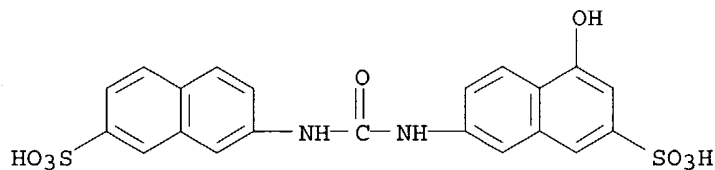
RN 207974-37-6 HCAPLUS
 CN 2-Naphthalenesulfonic acid, 4-hydroxy-7-[[[(2-naphthalenylamino)carbonyl]amino]- (9CI) (CA INDEX NAME)



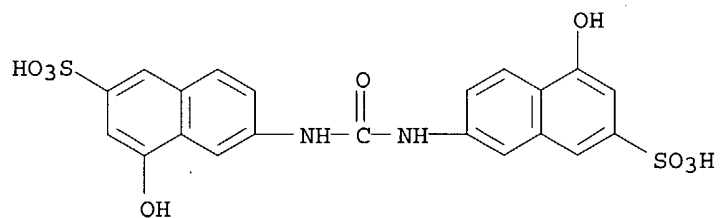
RN 207974-38-7 HCAPLUS
 CN 1,3-Naphthalenedisulfonic acid, 7-[[[(5-hydroxy-7-sulfo-2-naphthalenyl)amino]carbonyl]amino]- (9CI) (CA INDEX NAME)



RN 207974-39-8 HCAPLUS
 CN 2-Naphthalenesulfonic acid, 4-hydroxy-7-[[[(7-sulfo-2-naphthalenyl)amino]carbonyl]amino]- (9CI) (CA INDEX NAME)

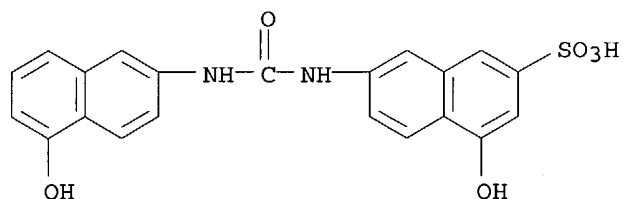


RN 207974-40-1 HCAPLUS
 CN 2-Naphthalenesulfonic acid, 4-hydroxy-6-[[[(5-hydroxy-7-sulfo-2-naphthalenyl)amino]carbonyl]amino]- (9CI) (CA INDEX NAME)



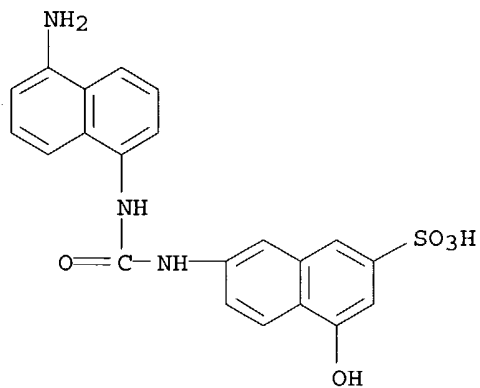
RN 207974-41-2 HCAPLUS

CN 2-Naphthalenesulfonic acid, 4-hydroxy-7-[[[(5-hydroxy-2-naphthalenyl)amino]carbonyl]amino]- (9CI) (CA INDEX NAME)



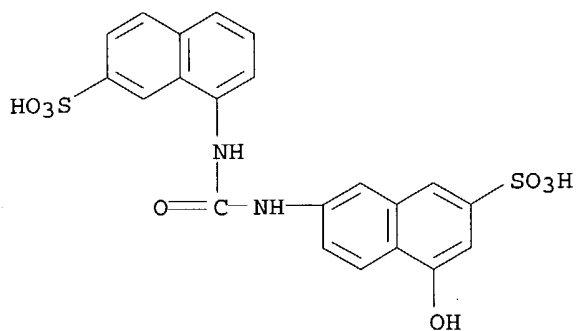
RN 207974-43-4 HCAPLUS

CN 2-Naphthalenesulfonic acid, 7-[[[(5-amino-1-naphthalenyl)amino]carbonyl]amino]-4-hydroxy- (9CI) (CA INDEX NAME)

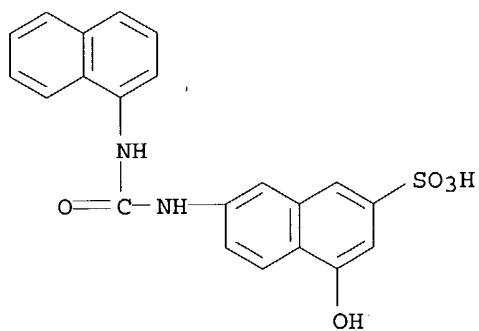


RN 215785-49-2 HCAPLUS

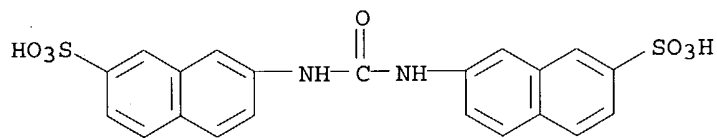
CN 2-Naphthalenesulfonic acid, 4-hydroxy-7-[[[(7-sulfo-1-naphthalenyl)amino]carbonyl]amino]- (9CI) (CA INDEX NAME)



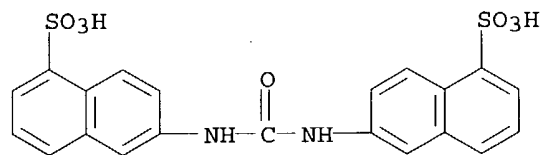
RN 215785-50-5 HCAPLUS
 CN 2-Naphthalenesulfonic acid, 4-hydroxy-7-[[[(1-naphthalenylamino)carbonyl]amino]- (9CI) (CA INDEX NAME)



RN 215786-14-4 HCAPLUS
 CN 2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



RN 215786-15-5 HCAPLUS
 CN 1-Naphthalenesulfonic acid, 6,6'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)

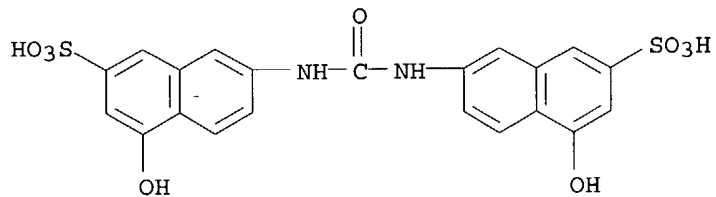


IT 134-47-4P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of N,N'-bis(hydroxysulfonaphthyl)ureas and analogs as

HIV reverse transcriptase and integrase inhibitors)

RN 134-47-4 HCAPLUS

CN 2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis[4-hydroxy- (9CI)
(CA INDEX NAME)



REFERENCE COUNT:

9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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1 309931-84-8/BI
1 309931-85-9/BI
1 309931-86-0/BI
1 309931-87-1/BI
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L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:654173 CAPLUS

DOCUMENT NUMBER: 141:342930

TITLE: In vitro and in vivo prevention of HIV protease inhibitor-induced insulin resistance by a novel small molecule insulin receptor activator

AUTHOR(S): Cheng, Mingshan; Chen, Seiyu; Schow, Steven R.; Manchem, Vara Prasad; Spevak, Wayne R.; Cristobal, Cristina P.; Shi, Songyuan; Macsata, Robert W.; Lum, Robert T.; Goldfine, Ira D.; Keck, James G.

CORPORATE SOURCE: Telik, Inc., Palo Alto, CA, 94304, USA

SOURCE: Journal of Cellular Biochemistry (2004), 92(6), 1234-1245

CODEN: JCEBD5; ISSN: 0730-2312

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Protease inhibitor (PI) therapy for the treatment of patients infected with human immunodeficiency virus is frequently associated with insulin resistance and diabetic complications. These adverse effects of PI treatment result to a large extent from their inhibition of insulin-stimulated glucose transport. Insulin receptor (IR) activators that enhance the insulin signaling pathway could be effective in treating this resistance. However, there are no agents reported that reverse inhibition of insulin action by PIs. Herein, we describe the effects of TLK19781. This compound is a non-peptide, small mol., activator of the IR. We now report in cultured cells, made insulin resistant HIV by PI treatment, that TLK19781 both increased the content of insulin-stimulated GLUT4 at the plasma membrane, and enhanced insulin-stimulated glucose transport. In addition, oral administration of TLK19781 with the PI, indinavir improved glucose tolerance in rats made insulin resistant. These results suggest, therefore, that IR activators such as TLK19781 may be useful in treating the insulin resistance associated with PIs.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:862665 CAPLUS

DOCUMENT NUMBER: 138:163274

TITLE: Regulation of Insulin Receptor Function by a Small Molecule Insulin Receptor Activator

AUTHOR(S): Pender, Celia; Goldfine, Ira D.; Manchem, Vara Prasad; Evans, Joseph L.; Spevak, Wayne R.; Shi, Songyuan; Rao, Sandhya; Bajjalieh, Sonia; Maddux, Betty A.; Youngren, Jack F.

CORPORATE SOURCE: University of California, Mount Zion Medical Center, San Francisco, CA, 94143-1616, USA

SOURCE: Journal of Biological Chemistry (2002), 277(46), 43565-43571

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compounds*

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In type 2 diabetes mellitus, impaired insulin signaling leads to hyperglycemia and other metabolic abnormalities. TLK19780, a non-peptide small mol., is a new member of a novel class of anti-diabetic agents that function as activators of the insulin receptor (IR) β -subunit tyrosine kinase. In HTC-IR cells, 20 μ M TLK19780 enhanced maximal insulin-stimulated IR autophosphorylation 2-fold and increased insulin sensitivity 2-3-fold. In contrast, TLK19780 did not potentiate the action of insulin-like growth factor-1, indicating the selectivity of TLK19780 toward the IR. The predominant effect of TLK19780 was to increase the number of IR that underwent autophosphorylation. Kinetic studies indicated that TLK19780 acted very rapidly, with a maximal effect observed 2 min after addition to insulin-stimulated cells. In 3T3-L1 adipocytes, 5 μ M TLK19780 enhanced insulin-stimulated glucose transport, increasing both the sensitivity and maximal responsiveness to insulin. These studies indicate that at low micromolar levels small IR activator mols. can enhance insulin action in various cultured cells and suggest that this effect is mediated by increasing the number of IR that are tyrosine-phosphorylated in response to insulin. These studies suggest that these types of mols. could be developed to treat type 2 diabetes and other clin. conditions associated with insulin resistance.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:794315 CAPLUS

DOCUMENT NUMBER: 137:289023

TITLE: Method for determining whether a compound is an insulin receptor kinase activator

INVENTOR(S): Manchem, Prasad V. S. V.; Lum, Robert T.; Schow, Steven R.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 6 pp., Cont.-in-part of U. S. Ser. No. 977,059.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

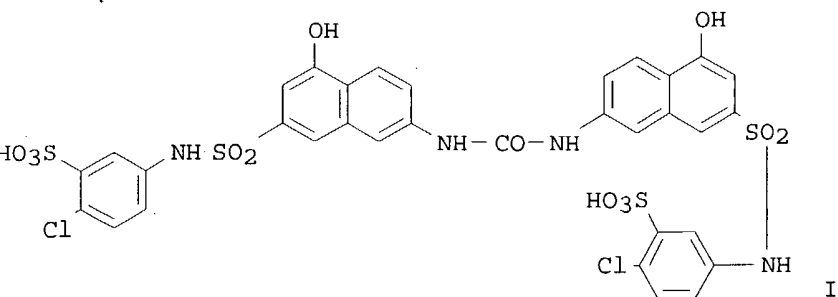
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002151542	A1	20021017	US 2002-115595	20020402
US 6528037	B2	20030304		
US 2002061927	A1	20020523	US 2001-977059	20011011
WO 2003085127	A2	20031016	WO 2003-US9805	20030331
WO 2003085127	A3	20040108		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-239636P P 20001011
US 2001-977059 A2 20011011
US 2002-115595 A 20020402

GI



AB A method is provided for determining whether a compound is an insulin receptor kinase activator. The methodol. of the invention comprises administering the compound to a non-human mammal concurrently treated with an HIV protease inhibitor; administering glucose to the mammal; and measuring the level of plasma insulin or plasma glucose in the mammal, where a reduced level of plasma insulin or plasma glucose in the mammal compared to a comparable mammal that has been treated with the HIV protease inhibitor and administered the glucose, but not administered the compound, indicates that the compound is an insulin receptor kinase activator. Reversal of protease inhibitor-mediated insulin resistance in normal rats by I (preparation included) is described.

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:293499 CAPLUS

DOCUMENT NUMBER: 136:304094

TITLE: Insulin receptor activators for the treatment of metabolic disorders in humans resulting from treatment of HIV infection with HIV protease inhibitors

INVENTOR(S): Manchem, Prasad V. V. S. V.; Lum, Robert T.; Schow, Steven R.

PATENT ASSIGNEE(S): Telik, Inc., USA

SOURCE: PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030514	A2	20020418	WO 2001-US42733	20011010
WO 2002030514	A3	20030731		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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FR 2814953	A1	20020412	FR 2001-13040	20011010
CA 2421622	AA	20020415	CA 2001-2421622	20011010
AU 2002011922	A5	20020422	AU 2002-11922	20011010
EP 1355698	A2	20031029	EP 2001-980019	20011010
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004510831	T2	20040408	JP 2002-533952	20011010
PRIORITY APPLN. INFO.: US 2000-239636P P 20001011				
WO 2001-US42733 W 20011010				

OTHER SOURCE(S): MARPAT 136:304094

AB The invention comprises the use of insulin receptor activating compds., optionally in conjunction with insulin, for the treatment of HIV protease inhibitor-induced metabolic disorders. Any insulin receptor activating

Instant invention

comps. suitable for the practice of the invention and other addnl.
dinaphthalene urea derivs. are disclosed. Methods of treating a person
suffering from HIV protease inhibitor-induced metabolic disorders such as
lipodystrophy, hypertriglyceridemia, insulin resistance, hyperglycemia,
diabetes and ketoacidosis are also provided.

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:842102 CAPLUS

DOCUMENT NUMBER: 134:17320

TITLE: Preparation of novel dinaphthyl ureas as glucose
uptake enhancers

INVENTOR(S): Spevak, Wayne; Lum, Robert T.; Shi, Songyuan; Mancham,
Prasad; Kozlowski, Michael R.; Schow, Steven R.

PATENT ASSIGNEE(S): Telik, Inc., USA

SOURCE: PCT Int. Appl., 120 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

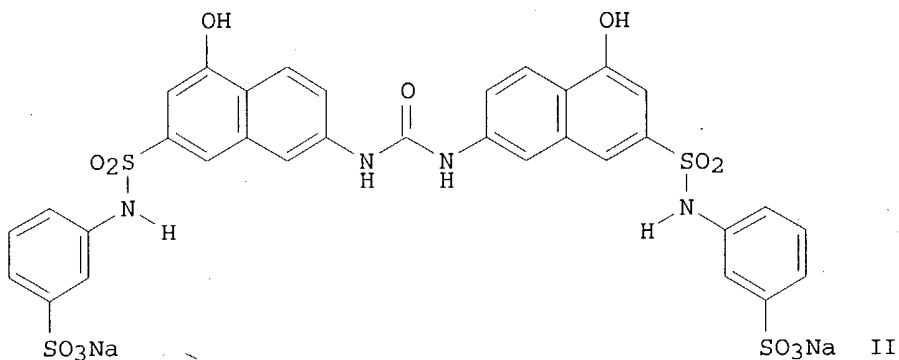
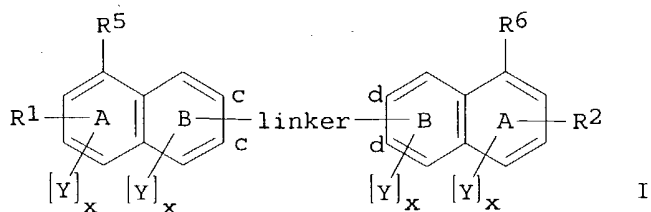
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071506	A2	20001130	WO 2000-US14644	20000525
WO 2000071506	A3	20010809		
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CA 2374225	AA	20001130	CA 2000-2374225	20000525
EP 1181271	A2	20020227	EP 2000-936360	20000525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200103409	T2	20020521	TR 2001-200103409	20000525
BR 2000011550	A	20020604	BR 2000-11550	20000525
US 6458998	B1	20021001	US 2000-579279	20000525
JP 2003500381	T2	20030107	JP 2000-619763	20000525
NZ 515743	A	20030829	NZ 2000-515743	20000525
AU 776438	B2	20040909	AU 2000-51684	20000525
ZA 2001009641	A	20030224	ZA 2001-9641	20011122
NO 2001005713	A	20011220	NO 2001-5713	20011123
US 2003135063	A1	20030717	US 2002-237583	20020906
PRIORITY APPLN. INFO.:				
			US 1999-136128P	P 19990526
			US 2000-579279	A1 20000525
			WO 2000-US14644	W 20000525

OTHER SOURCE(S): MARPAT 134:17320

GI



AB The title compds. [I; R1, R2 = SO₂NR₇2, CONR₇2, NR₇SO₂R₇, etc.; R5, R6 = H, alkyl, CN, etc.; R7 = H, alkyl, aryl, etc.; Y = a non-interfering substituent which is not linked to the naphthalene ring via an azo or amide linkage; x = 0-2; the linker connects a carbon designated as c to a carbon designated as d, and is NR₃C(:K)NR₄ (wherein K = O, S, NH, etc.; R₃, R₄ = H, alkyl; R₃, R₄ together = (CH₂)₂, (CH₂)₃, (CH₂)₄, etc.), N:C(NR₁₁2)NR₄ (R₁₁ = H, CN, alkyl); NR₃C(NR₁₁2):N, etc.], useful for treating conditions associated with hyperglycemia, especially Type II diabetes, were prepared and formulated. E.g., a multi-step synthesis of the urea II which produced a 13% decrease in blood glucose levels, a 42% decrease in plasma insulin levels, and a 15% decrease in plasma triglyceride levels in the ob/ob mouse model of Type II diabetes, was given. The compds. I are useful in stimulating the kinase activity of the insulin receptor, activating the insulin receptor, and stimulating the uptake of glucose.